

PATENT  
Attorney Docket No. HOGAN-06650

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re Application of: Kirk Hogan  
Serial No.: 09/976,423  
Filed: 10/12/01  
Entitled: Methods and Compositions for Perioperative Genomic Profiling

Group No.: 1634  
Examiner: Goldberg

**TRANSMITTAL OF APPEAL BRIEF  
(PATENT APPLICATION - 37 CFR § 192)**

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Dated: January 8, 2004

By:

  
Mary Ellen Ware

Sir or Madam:

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on **01/08/04**.

**2. STATUS OF APPLICANT**

This application is on behalf of

a small entity.

A verified statement has already been filed.

**3. FEE FOR FILING APPEAL BRIEF**

Pursuant to 37 CFR § 1.17(g), the fee for filing the Appeal Brief is:

**Fee for Filing Appeal Brief \$165.00**

**3. NOTICE OF APPEAL**

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**4. EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

Applicant petitions for a three month extension of time under 37 CFR § 1.136  
(fees: 37 CFR §§ 1.17(a)-(d)).

**Fee for Extension of Time \$475.00**

**5. TOTAL FEE DUE**

The total fee due is:

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Extension fee (if any) \$475.00

**TOTAL FEE DUE \$805.00**

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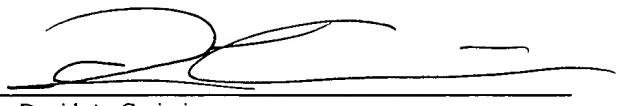
**6. FEE PAYMENT**

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**7. FEE DEFICIENCY**

If any additional fee is required, charge Account No. **08-1290**.

Dated: January 8, 2004

  
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**PATENT**  
Attorney Docket No. **HOGAN-06650**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

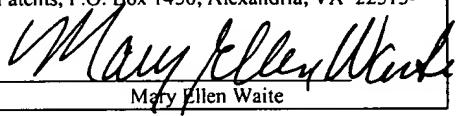
In re Application of: Kirk Hogan  
Serial No.: 09/976,423 Group No.: 1634  
Filed: 10/21/2001 Examiner: J.A. Goldberg  
Entitled: Methods and Compositions for Perioperative Genomic Profiling

**APPELLANTS' BRIEF**  
**APPEAL NO.:**

**CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. § 1.8(a)(1)(i)(B)**

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DATED - JAN 8, 2004

By:   
Mary Ellen Waite

**Mail Stop Appeal Brief - Patents**  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Madam/Sir:

This Brief is in furtherance of the Notice of Appeal mailed herewith.

The fees required under SS 1.17(h) and any required Petition for Extension of time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

A request for a three month extension of time to extend the time of filing from October 8, 2003 to January 8, 2003 is attached.

**This Brief is transmitted in triplicate. [37 CFR SS 1.192(a).]**

This Brief contains these items under the following headings and in the order set forth below [37 CFR SS 1.192(c)]:

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## **I. REAL PARTY IN INTEREST**

The real party in interest is the inventor of record, Kirk Hogan.

## **II. RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences known to the Appellant or to the Appellant's legal representative.

## **III. STATUS OF CLAIMS**

Claims 1-23 were filed in the original application. During prosecution of the application, Claims 1- 23 were cancelled and claims 24-44 were added in a previous amendment. Claims 24-44 were cancelled, and Claims 45-71 were added in the Amendment and Response to Office Action filed April 14, 2003. Claims 69 and 70 were withdrawn from consideration by the Examiner in the Final Office Action of July 8, 2003. Claims 45-68 and 71 have been rejected by the Examiner in the Final Office Action dated July 8, 2003. No other claims are pending. Therefore, Claims 45-68 and 71 are pending in this appeal. Appellant appeals the Final Office Action of July 8, 2003.

The Claims, as they now stand, are set forth in Appendix A.

## **IV. STATUS OF THE AMENDMENTS**

With respect to the amendments of the Claims, Appellant's Amendment and Response of September 8, 2003 has not been entered by the Examiner. Appellant therefore submits as Appendix B the Amendment and Response to the Final Office

Action of July 8, 2003 (filed September 8, 2003) for review with this Appeal Brief, and requests that the amendment be entered herewith.

## **V. SUMMARY OF THE INVENTION**

The present invention relates to kits for perioperative genomic screening of patients for genetic markers indicative of responses to anesthesia, and to other surgical or operative treatments and procedures. In current clinical practice, there is no technology available that provides the information of the perioperative genomic profile kits of the present invention. In the past, screening tests of a patient's phenotype (e.g., blood and urinalysis, EKG, and chest X-ray) were routinely performed prior to surgery. However, the present-day procedure for heritable disorders does not look at genetic information and is limited to asking a patient if they or their family members have had any previous difficulties with anesthesia or surgery. Sometimes, but not always, a physical exam is also performed. The use of laboratory phenotypic tests for patients prior to surgery has generally been reduced or eliminated. Reasons for elimination include the inaccuracy and lack of specificity of the phenotypic tests, the aggregate costs of heterogenous phenotypic screening panels, and uncertainty as to how to alter treatment course of action in response to results. Accordingly, contemporary anesthesiology and surgery textbooks emphasize that recent studies indicate a lack of benefit from routine phenotypic testing as a method of assessing patients preoperatively, and stress that cost-benefit strategies can only be justified when laboratory testing is reduced to that indicated by history-taking.

The perioperative genomic profile kits of the present invention stand in direct contrast to the panels of phenotypic tests currently available. In the present invention, genetic alleles are tested in ensemble according to selection categories and criteria taught by the present invention to construct a personalized perioperative genomic profile. The perioperative genomic profile kits of the present invention may be used, for example, to establish the subject's prognosis or odds of survival, to select the safest and most efficacious anesthetic regimen and surgical procedure, to determine the optimal level of post-surgical monitoring, and to begin life-saving intervention as soon as possible. The perioperative genomic profile kits of the present invention thereby solve many of the problems described above that have led practitioners away from preoperative phenotypic

testing. The perioperative genomic profile kits of the present invention are cost and time effective. Genomic markers are selected for inclusion in the kit, for example, by virtue of their analytical validity (accuracy, specificity, and predictive value), clinical validity and clinical utility. The perioperative genomic profile kits of the present invention thus allow, for example, for the individualization of treatment options for each subject undergoing a surgical procedure. In this fashion, the present invention provides a novel diagnostic tool currently unavailable in the surgical field, enabling solutions for problems that have no available alternatives. In the absence of any competing technology for quantifying subject's genetic contributors to perioperative risk, the present invention provides life- and cost-saving information to caregivers on an accelerated and amplified scale relative to current diagnostics.

## **VI. ISSUES**

There are three issues involved in the present appeal:

Issue 1 – Whether the Specification provides support for Claims 46-48 and 71 under 35 U.S.C. 112, first paragraph.

Issue 2 – Whether Claims 45-68, 71 are definite under 35 U.S.C. 112, second paragraph.

Issue 3 – Whether Claims 45, 48-68, and 71 are patentable under 35 U.S.C. 102(b) in view of:

- a) 1997 Boehringer Mannheim Biochemicals Catalog.
- b) 1996 Perkin Elmer, PCR Systems, Reagents & Consumables catalog.
- c) 1993 Applied Biosystems Catalog.

## **VII. GROUPING OF CLAIMS**

Each Claim stands alone. Each Claim has separate limitations and must be considered independently.

Independent Claim 45 specifies a kit for generating a perioperative genomic profile for a subject, comprising reagents capable of detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*,

*F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$ ; and instructions for using said kit for generating said perioperative genomic profile for said subject.*

Dependent Claim 46 specifies the kit of Claim 45, wherein the kit comprises a computer readable medium comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

Dependent Claim 47 specifies the kit of Claim 46, wherein the kit comprises a computer readable medium comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

Dependent Claim 48 specifies the kit of Claim 45, wherein the kit comprises instructions that comprise a decision tree that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

Dependent Claim 49 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

Dependent Claim 50 specifies the kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

Dependent Claim 51 specifies the kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

Dependent Claim 52 specifies the kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

Dependent Claim 53 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

Dependent Claim 54 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

Dependent Claim 55 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

Dependent Claim 56 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

Dependent Claim 57 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

Dependent Claim 58 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

Dependent Claim 59 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

Dependent Claim 60 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

Dependent Claim 61 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

Dependent Claim 62 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

Dependent Claim 63 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

Dependent Claim 64 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

Dependent Claim 65 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

Dependent Claim 66 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

Dependent Claim 67 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

Dependent Claim 68 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

Independent Claim 71 specifies a perioperative genomic profile kit having component parts capable of being assembled for detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject, and thereby providing a subject-specific clinical pathway for said subject, comprising a decision tree that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

Because each of the independent claims have different limitations, they do not stand or fall together. Rather they must be evaluated separately.

## **VIII. ARGUMENT**

### **A. The Specification Fully Supports The Claims**

In the Final Office Action of July 8, 2003, the Examiner has rejected Claims 46-48, and 71 under 35 U.S.C. 112, first paragraph:

“Claims 46-48, 71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment fails to point to any support in the specification for the newly added language. However, the specification does not appear to describe or discuss “a computer readable medium” and a “decision tree”. The concept of “a computer readable medium” and a “decision tree” does not appear to be part of the originally filed invention. Therefore “a computer readable medium” and a “decision “tree” constitutes new matter. Applicant is required to cancel the new matter in reply to this office action.” (Final Office Action July 8, 2003, page 3.) (Emphasis added.)

In the Amendment and Response to Final Office Action Dated July 8, 2003 Appellant respectfully disagreed with the Examiner. To the contrary, the Specification provides ample, specific and detailed support for the Claims. Several non-limiting examples directly quoted from the Specification were provided to the Examiner (Amendment and Response to Final Office Action Dated July 8, 2003, pages 7-9):

“Assays for detection of polymorphisms or mutations fall into several categories, including, but not limited to direct sequencing assays, fragment polymorphism assays, hybridization assays, and computer based data analysis.” (Specification, II. “Assays for Generating Genomic Profiles”, page 40. Emphasis added.)

“In some embodiments of the present invention, perioperative genomic profiles are generated using computer-based data analysis of a genetic information sample (e.g., stored nucleic acid sequence information). A sample is collected from a subject at anytime (e.g., at birth), sequence information is generated (e.g., through DNA sequencing), and the information is stored (e.g., as digital information on a portable chip). During the perioperative period, the subject's sequence information is scanned by a computer program for the pre-selected markers. A report (e.g., a perioperative genomic profile) is generated.” (Specification II.E., “Computer-Based Data Analysis”, page 49. Emphasis added.)

“In some embodiments of the present invention, the data is generated, processed, and/or managed using electronic communications systems (e.g., Internet-based methods). In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease).” (Specification, III. “Analysis and Delivery of Data”, page 50. Emphasis added.)

“Where the sample comprises previously determined genetic information (e.g., sequence information, SNP or mutation information, etc.), the information may be directly sent to the genomic profiling service by the subject (e.g., a information card containing the genetic information may be scanned by a computer and the data transmitted to a computer of the genomic profiling center using an electronic communication systems). Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo.” (Specification, III. “Analysis and Delivery of Data”, pages 50-51. Emphasis added.)

“In some embodiments, the process of selecting markers, performing detection assays, and distributing data to subjects and clinicians is organized by an integrated electronic (e.g., web-based) system.” (Specification, “Detailed Description of the Invention”, page 30. Emphasis added.)

“The present invention contemplates any method capable of receiving, processing, and transmitting the information to and from medical personal and subject.” (Specification III., “Analysis and Delivery of Data”, page 50. Emphasis added.)

“In some preferred embodiments of the present invention, the information generated by perioperative genomic profiling is distributed in a coordinated and automated fashion.” (Specification III. “Analysis and Delivery of Data, page 49. Emphasis added.)

“The fate of the sample and genomic data is driven by the subject, who is given a menu (e.g. electronically) of choices. . . For example, using an electronic communication system, the central facility can provide data to the clinician, the subject,

or researchers. . . . In some embodiments, the subject may be able to directly access the data using the electronic communication system.” (Specification III. “Analysis and Delivery of Data, page 51. Emphasis added.)

“The data may be displayed to the clinician by any suitable method. For example, in some embodiments, the genomic profiling service generates a report that can be printed for the clinician (e.g., at the point of care) or displayed to the clinician on a computer monitor.” (Specification III., “Analysis and Delivery of Data”, page 51. Emphasis added.)

“The data generated by the assay may converted to a genomic profile in a computer system of the emergency vehicle or may be transmitted to distant computer system for processing.” (Specification III., “Analysis and Delivery of Data, page 51. Emphasis added.)

In the Advisory Action of October 16, 2003 the Examiner has completely ignored this abundant, specific and objective evidence of support in the Specification for Claims 45-48, and 71 and has failed to address or enter Appellant’s claim amendments that sought to utilize language in the claims more directly aligned to the language of the specification (although Appellant believes that the claim language of the both the original and amendment claims are properly supported by the specification). In these amendments, which Appellant requests be entered with this Appeal, Claims 46-48 and 71 are amended to recite “computer program” and “information to optimize perioperative care.”(Amendment and Response to Final Office Action Dated July 8, 2003, page 9.).

Both the original claims and the amended claims are clearly supported in the specification. The Examiner’s failure to address Appellant’s evidence and argument is error. Appellant is entitled to have its arguments considered; yet no such consideration was given. For the reasons discussed in Section C, below, consideration of the argument, with or without entry of the amendment, results in at least claims 46 and 47 being allowed. Thus, failure to consider the arguments (and/or amendments) prejudices Appellant.

## **B. The Claims are Definite**

In the Final Office Action of July 8, 2003 the Examiner has rejected Claims 45-68 and 71 under 35 U.S.C. 112, second paragraph:

“Claims 45-68, 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.”

“The response asserts that the claimed reagents provide agents for detecting the variant alleles using the range of different technologies described in the specification.” This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require that the reagents in fact detect the presence of the variant alleles. The claim could be amended to recite “reagents which detect . . .” to overcome the rejections.” (Page 4.) (Emphasis added.)

In the Amendment and Response to Final Office Action Dated July 8, 2003, Appellant respectfully disagreed with the Examiner. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Appellant amended Claims 45 and 71 to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively as requested by the Examiner.

In the Advisory Action of October 16, 2003, the Examiner did not address the amendments which the Examiner had suggested with particularity in the Final Office Action of July 8, 2003. In view of the above, Appellant requests the Board withdraw this rejection and enter the amendments, as there appears to be no issue here when the amendments are entered.

#### **C. The Examiner has Improperly Failed to Enter Appellant’s Amendments**

Claims 46 and 47 are only rejected under the 112 grounds discussed in Sections A and B, above. They are not rejected under the prior art. Appellants amendments filed with the Response to the Final Office Action address the Examiners concerns: in one case changing the terminology as suggested by the Examiner to overcome an indefiniteness rejection and in the other case substituting the term “computer

program" for "computer readable medium" to overcome a new matter rejection. That these amendments overcome the rejections is unquestionable for the reasons discussed in Sections A and B, above. As these are the only bases for rejection of Claim 46 and 47, the amendments unquestionably place the claims in position for allowance. Therefore, amendments should have been entered and the claims should have been allowed. The only basis in the Advisory Action cited by the Examiner for failing to enter the amendments is the checked box, "[the amendments] raise new issues that would require further consideration and/or search (see NOTE below)", with the corresponding note simply saying that the arguments are moot—providing no reasons why this is the case. The Examiner has not pointed to any basis why new searches would be required (indeed - they should not be since the claims that were pending prior to the Final rejection contained computer elements, and the Examiner was aware of extensive prior art related to the invention from this application and parent application #09/613,887; a copy of form 1449 is attached hereto at Tab C), or why further consideration is required (the claims unquestionably find support in the specification, clearly rendering the new matter rejection moot without further consideration). Had the amendments been entered, the claims would be allowed and Sections A, B, and C of the Appeal would be unnecessary.

#### **D. The Cited References do not Anticipate the Claims**

In the Final Office Action of July 8, 2003, the Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. For clarity and efficiency, because their defects as prior art are shared, and because the Examiner has cut and pasted verbatim from the Boehringer Mannheim text of the Final Office Action of July 8, 2003 to the Perkin Elmer and Applied Biosystems texts (without even changing "Boehringer Mannheim" to "Perkin Elmer" (page 12) or "Applied Biosystems" (page 17)), the three references will be addressed together.

The text of 35 U.S.C. 102 quoted by the Examiner reads:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or

in public use or on sale in this country, more than one year prior to the date of application in the United States.

(Final Office Action July 8, 2003, page 5).

Appellant respectfully asserts that the references cited by the Examiner strikingly fail to meet this standard of anticipation. To the contrary, the catalog pages do not teach a perioperative genomic profile kit. The catalog pages do not teach reagents which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChe*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . The catalog pages do not teach instructions for using a kit for generating a perioperative genomic profile. The catalog pages do not teach computer programs or information to optimize perioperative care. The prior art references do not teach a kit having components that provide a subject-specific clinical pathway of medical intervention if used.

In the Amendment and Response to Final Office Action Dated July 8, 2003, Appellant reminded the Examiner that the Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."<sup>1</sup>

Appellant respectfully submits that not one of the catalog references cited by the Examiner teach each and every element as set forth in the claims.

**1. The Claims Require Detection of Specific Variant Alleles - The Examiner's Cited Catalog Pages Do Not Teach this Element**

In the Appellant's Amendment and Response to Office Action Dated January 21, 2003 (filed April 14, 2003), Appellant pointed out to the Examiner that:

"None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two

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<sup>1</sup> *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

or more genes from the group of genes of the present invention.” (Amendment and Response to Office Action of January 21, 2003, filed April 14, 2003, page 9).

In the Final Office Action of July 8, 2003 the Examiner argues:

“This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require detection of the variant alleles.” (Final Office Action July 8, 2003, page 8).

Appellant respectfully disagrees. To the contrary, the catalog pages cited by the Examiner have no teaching or suggestion to use variant alleles of two or more of the claimed genes. Thus, none of the cited references teach or suggest kits having reagents capable of detecting the specific variant alleles as recited in the claims. Hence, the Examiner has not responded to the main point of Appellant’s rebuttal.

However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Appellant had amended Claims 45 and 71 as suggested by the Examiner to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively.

In the Examiner’s Advisory Action of October 16, 2003, the Examiner fails to consider these amendments that the Examiner suggested with particularity. In view of the above, Appellant requests the Board withdraw this rejection and enter the amendments or otherwise pass the original claims to allowance as the prior art fails to teach the elements of either the original claims or the amended claims.

## **2. Instructions are Functional Components of the Claimed Kits and Cannot be Ignored**

In the Final Office Action of July 8, 2003 the Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one

of the three prior art references recite the limitation “instructions for using said kit for generating said perioperative genomic profile for said subject.” as recited in Claim 45. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring this element. (Final Office Action July 8, page 8).

**a. The Examiner’s Rejection of Instructions as Functional Components of the Claimed Kits is Procedurally Defective**

The Examiner has never argued in the Office Action of December 2, 2002, in the Office Action of January 21, 2003, in the Final Office Action of July 8, 2003, or in the Advisory Action of October 16, 2003 that the cited catalog references teach instructions for the operation of a perioperative genomic profiling kit. Hence, the Examiner’s argument that the cited art references anticipate the present invention under 35 U.S.C., 102(b) is procedurally defective, and must be withdrawn.

Rather, the Examiner argues whether instructions for generating a perioperative genomic profile are a legitimate claim element, not whether instructions for the operation of the kit are anticipated by the Examiner’s references. (Final Office Action of July 8, 2003, pages 9-11.) To the contrary, if instructions are a legitimate claim element, then there is no question that the prior art cited by the Examiner fails to teach or suggest the limitation. Nor has the Examiner asserted otherwise. Therefore, the claims are allowable if the instructions are an element of the Claims. Incontrovertibly they are.

**b. The Examiner Confuses Instructions for the Operation of a Kit with a “Statement of Intended Use” and Has Failed to Properly Respond to Appellant’s Response**

In the Advisory Action of October 16, 2003 the Examiner argues:

“The response asserts that the intended use which is recited on the instructions with printed instructions for use. (sic) This argument has been thoroughly addressed in the final rejection.” (Page 3).

Appellant submits that it is impossible to know what the Examiner means in the first sentence since the Examiner has failed to proofread the sentence. Appellant therefore assumes that the Examiner is reiterating the same arguments as those to be found in the Final Office Action of July 8, 2003 (pages 9-11) in which the Examiner confuses instructions for the operation of a kit with a statement of intended use. For example, the Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). (Office Action 7/8/2003, page 10).

If this is in fact what the Examiner has meant in the Advisory Action of October 16, 2003, then the Appellant’s argument has not been thoroughly addressed in the Appellant’s Amendment and Response to the Office Action of January 21, 2003, or even addressed at all in the Appellant’s Amendment and Response to Final Office Action Dated July 8, 2003.

For example, in the Final Office Action of July 8, 2003, the Examiner argues:

“*In re Haller* states that, in accordance with the patent statutes, an article or composition of matter, in order to be patentable, must not only be useful but must be new. *If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition regardless of the use for which it is intended.*” (Final Office Action July 8, 2003, page 9. Italics in original. Underline added.)

However, *In re Haller* is of no relevance to rejection of the present invention. Instructions are not a “statement of intended use”, nor are instructions “mere re-labelling” (*In re Haller*, 403). In citing *In re Haller*, the Examiner mistakenly confuses operational

kit instructions with “an admittedly old compound, labelled for a new use as an insecticide”, (*id* at 403), while *In re Haller* itself does not. Indeed, the term “instructions” and “kit” fail to appear anywhere in the text of *In re Haller*.

In the Amendment and Response to Office Action of January 21, 2003, Appellant pointed out that the claimed instructions are novel, physical components dictating the manipulations of physical objects and activities which, as components of the claimed kits, implement a set of actions to accomplish a useful, concrete and tangible result. (Page 11.) Under some embodiments of the presently invention, instructions that direct, for example, a treatment course of action utilize physically organized data structures for two or more assays, which are not fixed or determinate beforehand. A patient’s preferred clinical pathway cannot properly be executed in advance absent the results of the assay as instructed. Instructions that cause and direct a particular treatment course of action utilize results from two or more genotypes. A combination of markers may well instruct one course of action rather than another.

In the Final Office Action of July 8, 2003, and in the Advisory Action of October 16, 2003, the Examiner has conspicuously failed to respond to these factual assertions. Indeed, the Examiner concedes in the Final Office Action of July 8, 2003 that:

“The instructions are used to describe how the kit is intended to be used.”

(Final Office Action of July 8, 2003, page 9. Emphasis added).

Nevertheless, in the Final Office Action of July 8, 2003 and the Advisory Action of October 16, 2003 the Examiner continues to confuse *In re Haller*’s “the use for which it is intended” (i.e. a statement of the kit’s purpose), with “how the kit is intended to be used”, i.e. the claimed and patentable instructions for operation of the present invention that embody functional components, interacting with other components of the claimed kits, in novel modes of cooperation, thereby permitting the kit’s functionality to be realized. (Amendment and Response to Office Action January 21, 2003, page 11.) In the Amendment and Response to Final Office Action of July 8, 2003 Appellant explained to the Examiner that the instructions of Claims 45 - 68 are physical component parts of the Claims (page 13). For example, a claim to “A system of doing X, comprising component

Y" is anticipated by prior art that discloses component Y for purposes other than X (i.e., use X is a statement of use the does not impart patentable weight to the claim). However, a claim that recites "A system comprising component Y and component Z, wherein component Z is configured to permit component Y to find use in process X" is patentable if the prior art does not teach the use of component Y in process X, or does not teach the use of component Z that is configured to facilitate the use of Y for X. The present claims represent the latter rather than the former example.

Contrary to thoroughly addressing these facts, the Examiner has been mute in response. In view of the above, Appellant requests that the Board direct the Examiner to respond to the Appellant's rebuttal, or to withdraw the rejections.

**c. The Examiner has Improperly Applied the Law of *In re Gulack*, Which Stands for the Patentability of the Present Invention**

In the Advisory Action of October 16, 2003 the Examiner argues:

"Fourth, the response again asserts there is no case law or MPEP citation which is relevant such that the examiner has made up and does not comport with the law. Applicant is respectfully requested to read *in re Gulack*."

*In re Gulack* was provided by the Appellant to the Examiner in support of the assertion that "... printed matter, in an article of manufacture claim, *can* be given "patentable weight."<sup>2</sup> (Original emphasis.) The CAFC in *In re Levin* holds:

"The only requirement that 35 U.S.C. §101 imposes as set forth in *In re Miller* is that a new and unobvious functional relationship must exist between the claimed combination of printed matter and other claimed elements. 418 F.2d at 1396, 164 U.W.P.Q. (BNA) at 49. For instance, as we have stated in *In re Gulack*, "the critical question is whether there exists any new and unobvious functional

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<sup>2</sup> *In re Miller* 57 C.C.P.A. 809; 418 F.2d 1392.

relationship between the printed matter and the substrate.” 703 F.2d at 1386, 217 U.S.P.Q. (BNA) at 404.<sup>3</sup>

Because novel, unobvious functional relationships clearly exist between the claimed instructions and substrate kits, the present invention easily surmounts the requirements of the *In re Gulack* test. An instruction is “An authoritative direction to be obeyed; an order”; instructions are “Detailed directions on procedure.” (The American Heritage Dictionary 3<sup>rd</sup> Edition, 1993). Clearly instructions do not “merely represent a statement of intended use” as the Examiner mistakenly alleges (Office Action of January 21, 2003, page 3). Hence, *In re Gulack* stands for exactly the opposite of the Examiner’s conclusory and unsupported assertion.

In the Final Office Action of July 8, 2003 the Examiner argues:

“However, in the case of *In re Gulack*, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself, which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed kit. The components of the kit remain fully functional absent the printed instructions for use.” (Final Office Action July 8, 2003, page 9)

The Examiner’s mischaracterizations of the present invention’s Claims are erroneous, and unsupported by any evidence, affidavit or other authority. To the contrary, the claimed instructions of the present invention clearly result in a structural and manipulative differences (*In re Casey*) between the manufacturer’s catalogs cited by the Examiner as prior art, and the articles and compositions of the present claims. Rather than remaining fully functional, the useful, concrete and tangible aspects of the kits of the present claims are not maintained after removal of “printed instructions for use”. In turn, the Examiner’s argument, raised for the first time in the Final Office Action of July 8, 2003, that “The components of the kit remain fully functional absent the printed

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<sup>3</sup> *In re Levin*, 107 F.3d 30 (Fed. Cir. 1997).

instructions for use.” represents a new and rebuttable ground of rejection that are unsupported by fact or evidence.

**d. The Examiner Improperly Fails to Consider the Declaration of Dr. Morris Waxler**

In the Advisory Action of October 16, 2003 the Examiner argues regarding the Declaration of Morris Waxler, Ph.D.:

“Affidavits and declarations submitted under 37 C.F.R. 1.132 and other evidence traversing rejections are considered timely if submitted:

...

(3) after final rejection and submitted

(i.) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection,”

(Advisory Action October 16, 2003, page 1).

The Examiner then makes the conclusory and unsupported assertion that the Declaration submitted with the September 8, 2003 Amendment and Response to Final Office Action “does not address a new ground of rejection.”

The Examiner is in error. In the Final Office Action of July 8, 2003 the Examiner makes the following new ground of rejection:

“The components of the kit remain fully functional absent printed instructions for use.” (Final Office Action July 8, 2003, page 9).

This ground for rejection is nowhere to be found in the Office Action of January 21, 2003. Therefore, the Examiner’s assertion is incontestably a new ground of rejection in the Final Office Action of July 8, 2003. Because the Examiner has made this new and baseless ground of rejection in the Final Office Action of July 8, 2003, under 37 C.F.R. 1.132(3)(i) Appellant is entitled to provide rebuttal evidence to the Examiner’s unsupported and conclusory speculation.

e. **Dr. Morris Waxler's Declaration Is Evidence of a Functional Relationship Between Operational Instructions and the Perioperative Genomic Profile Kits of the Present Invention which the Examiner has not Refuted**

The Examiner's unsupported statement that "the kit is unpatentable over the prior art because they function equally effectively with or without the instructions" is clearly erroneous. The Examiner repeats the identical mistake a second time in consideration of *In re Miller* stating:

"no functional relationship exists between the instructions and the other elements of the kit because the components of the kit are capable of functioning without the printed matter." (Final Office Action of July 8, 2003, page 10)

And:

"the kit is unpatentable over the prior art because they function equally effectively with or without instructions, and accordingly no functional relationship exists between the instructions for use and kit components." (Final Office Action of July 8, 2003 page 10).

To the contrary, as evidenced by the Declaration of Morris Waxler, Ph.D., instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. Dr. Waxler explains:

"The function of an *in vitro* genetic diagnostic kit depends on the instructions to be approved by the Food & Drug Administration; without instructions the *in vitro* genetic diagnostic kit is not considered to be functional by the Food & Drug Administration."

"an *in vitro* genetic diagnostic kit does not, and cannot, function equally effectively with or without instructions."

“The functional relationship between an *in vitro* genetic diagnostic kit and its operation is critical such that component instructions must undergo rigorous Food & Drug Administration scrutiny before the kit may be manufactured or marketed in order to assure its safety, efficacy and reliability.”

“Without Food & Drug Administration approved instructions for its operation an *in vitro* genetic diagnostic kit cannot be manufactured or marketed.”  
(Declaration of Morris Waxler, Ph.D. under 37 CFR §1.132, page 1)

Contrary to the Examiner’s unsupported assertions, the Food & Drug Administration recognizes the importance of the instructions to enable use of the reagents, and use of data obtained by use of the reagents in the hands of practitioners.

To sustain the rejection, the Examiner must present evidence (not conclusory statements or guesses) as to the lack of a functional relationship between the claimed instructions and other components of the kits. The Examiner’s rejection is not evidence. The Declaration is objective factual evidence. Examiner’s failure to consider the Declaration is defective as a matter of law. The Examiner is not in possession of countervailing factual evidence. Nor has the Examiner cited authority for the Examiner’s proposition that the test for a functional relationship is whether or not the components of the kit are capable of functioning without the printed matter. This is made-up law and does not reflect the actual law.

Therefore, Appellant requests the Board to withdraw the rejections or to direct the Examiner to consider the Declaration of Morris Waxler, PhD, and to withdraw the rejections.

**f. The Examiner’s “Physically or Chemically Affect the Chemical Nature” Standard is not the Law under 35 U.S.C. 102(b)**

In the Advisory Action of October 16, 2003 the Examiner argues:

“The third reason the response traverses is that the instructions both chemically and physically affect the chemical nature of the components of the kit. The final rejection has thoroughly responded to this arguments”. (Page 3.)

To the contrary the Examiner hasn't responded to the Appellant thoroughly or at all.

In the Final Office Action of July 8, 2003 the Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). (Final Office Action July 8, 2003, page 10).

In this assertion the Examiner makes numerous errors of both fact and law. First, the Examiner's arguments are conclusory, and unsupported by any citation to relevant case law, the MPEP, an affidavit, or other authority. Second, the Examiner confuses the “intended use which is recited on the instructions” with “printed instructions for use” Indeed the Examiner tacitly acknowledges the difference in distinguishing “intended use which is recited on the instructions”, from the body (how to) of the instructions. The claimed instructions of the present invention are not a “statement of intended use” (see above). Third, abundant examples are proffered in the Specification of instructions which both chemically and physically affect the chemical nature of the components of the kit (See Section I.B. “Criteria for Selection of Markers”, page 32, Section I.C. “Categories of Markers”, page 34, Experimental Example 1 “Perioperative Genomic Screening for Anesthesia Markers”, page 53, Experimental Example 2 “Generation of Genomic Profiles”, page 57).

Fourth, the Examiner puts forward no relevant case law, MPEP citation, affidavit or other authority in which the legal test for a functional relationship rests on whether operational instructions “physically or chemically affect the chemical nature of the components of the kit.” (Final Office Action July 8, 2003, page 10). This is a standard the Examiner has made up and does not comport with the law.

g. **The Examiner’s “Use for Other Purposes” Standard is not the law under 35 U.S.C. 102(b)**

The Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). Therefore the kit is unpatentable over the prior art . . .”  
(Office Action 7/8/2003, page 10).

Appellant asserts that whether or not “the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually)” has no legal bearing on patentability. To reach this peculiar and erroneous standard the Examiner has misinterpreted the Examiner’s own quoted law. For example, the Examiner argues:

“Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *In re Casey* 370 F.2d 576, 152, USPQ 235 (CCPA 1967); *In re Otto*, 312 F.2d 937, 938 136 USPQ 458, 459, (CCPA 1963). (Final Office Action of July 8, 2003, page 9)

Nothing in the cited case law elucidates a standard that “use for other purposes” defines improper functional language. As detailed above, instructions for the operation of a genomic profiling kit are not a “statement (or recitation) of intended use” as mischaracterized by the Examiner, regardless of whether the reagents have additional potential uses. In the Advisory Action of October 16, 2003, the Examiner argues:

”The response argues that the claims are not anticipated. The response asserts the examiners arguments are conclusory and unsupported by case law or the MPEP. The rejection of record cites both MPEP and case law on number of occasions (see pages 9-11, for example).” (Page 3.)

Appellant submits that the Examiner has misinterpreted the proper standard established by the MPEP and case law which - when considered - stands for the patentability of the present invention. Moreover, the Examiner impermissibly attempts to create a new legal standard, (i.e. whether “the components of the kit can be used by the skilled artisan for other purposes (wholly or individually)”). In view of the above, Appellant requests that the Board withdraw this rejection.

**h. The Examiner has Improperly Ignored Appellant’s Arguments Showing Distinguishing Features Between the Claims and the Prior Art**

In the Final Office Action of July 8, 2003 the Examiner argues:

“Applicant’s arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.” (page 11).

To the contrary, in the Amendment and Response to Office Action Dated January 21, 2003 (filed April 14, 2003), the Appellant expressly and specifically responded to the Examiner:

“None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention. None of the three references teaches categorical criteria for the selection of genes and variant alleles

of the present invention. None of the three references teaches generation of a perioperative genomic profile.” (page 9).

Although these facts were pointed out to the Examiner in the Amendment and Response to Final Office Action Dated July 8, 2003 (filed September 8, 2003), the Examiner made no response in the Advisory Action of October 16, 2003. Appellant therefore requests that the Board withdraw this rejection under 35 USC §102(b) or direct the Examiner to properly consider Appellant’s arguments.

For the numerous reasons cited above, the Examiner has improperly failed to consider the claim element of “instructions” in the claims. There is no dispute that this element is not found in the prior art. Because this element must be considered, for at least the reasons recited above, the rejections must be withdrawn and the claims passed to allowance.

### **3. The Examiner has Not Read Claim 71**

The Examiner has failed to properly address the patentability of Claim 71. It appears that the Examiner has misread the claim. In particular, the Examiner rejects Claim 71 on grounds that are irrelevant to the claim. Because the Examiner has failed to properly address the claim, Claim 71 must either be passed to allowance or a non-final office action must be issued on Claim 71.

In the Final Office Action of July 8, 2003 the Examiner has rejected Claim 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one of the three prior art references recites a perioperative genomic profile kit having component parts which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . Not one of the three prior art references recites a genomic profiling kit comprising information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention

for said subject, as recited in Claim 71. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring the absence of these limitations in the catalogs cited as prior art references. (Final Office Action July 8, page 8).

Importantly, although the Examiner groups rejection of Claim 71 with rejections of Claims 45, and 48-68 in consideration of “arguments directed to instructions” (Final Office Action of July 8, 2003, page 8), instructions for the operation of perioperative genomic profiling kits are not an element of Claim 71. In lumping Claim 71 into the other rejections, the claim elements unique to Claim 71 have been entirely ignored. Thus, the subject matter of Claim 71 has never been addressed by the Examiner. Because the Examiner has failed to properly address the claim, Claim 71 must either be passed to allowance or a non-final office action must be issued on Claim 71.

#### **E. CONCLUSION**

For the foregoing reasons, it is submitted that the Examiner’s rejection of Claims 45-68, and 71 was erroneous, and reversal of the rejection is respectfully requested. The Appellant requests that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Examiner.

Dated: 1/8/04



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Registration No. 42,395

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## **APPENDIX A: CLAIMS INVOLVED IN THE APPEAL**

45. A kit for generating a perioperative genomic profile for a subject, comprising:

- a) reagents capable of detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* ; and
- b) instructions for using said kit for generating said perioperative genomic profile for said subject.

46. The kit of Claim 45, further comprising a computer readable medium comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

47. The kit of Claim 46, further comprising a computer readable medium comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

48. The kit of Claim 45, wherein said instructions comprise a decision tree that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*,

*TNF $\alpha$*  and *TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

49. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

50. The kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

51. The kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

52. The kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

53. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

54. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

55. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

56. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

57. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

58. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

59. The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

60. The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

61. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

62. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

63. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

64. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

65. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

66. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

67. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

68. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

71. A perioperative genomic profile kit having component parts capable of being assembled for detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject and thereby providing a subject-specific clinical pathway for said subject, comprising a decision tree that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.



**PATENT**  
Attorney Docket No. **HOGAN-06650**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Kirk Hogan  
 Serial No.: 09/976,423 Group No.: 1634  
 Filed: 10/21/2001 Examiner: J.A. Goldberg  
 Entitled: Methods and Compositions for Perioperative Genomic Profiling

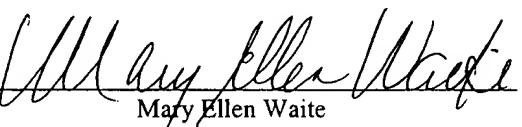
**AMENDMENT AND RESPONSE TO FINAL OFFICE  
ACTION DATED JULY 8, 2003**

Commissioner for Patents  
 P.O. Box 1450  
 Alexandria, VA 22313-1450

**CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(B)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 9-8-03

By:   
 Mary Ellen Waite

Madam:

The following communication is responsive to the Final Office Action mailed July 8, 2003, due on or before September 8, 2002 to provoke an Advisory Action. The Applicant respectfully requests reconsideration of the Application in view of the following amendment and remarks.

**I. IN THE CLAIMS:**

Claims 1 - 44 (previously cancelled).

45. (PRESENTLY AMENDED) A kit for generating a perioperative genomic profile for a subject, comprising:

- a) reagents ~~capable of detecting~~ which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* ; and
- b) instructions for using said kit for generating said perioperative genomic profile for said subject.

46. (PRESENTLY AMENDED) The kit of Claim 45, further comprising a computer ~~readable medium-~~ program comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

47. (PRESENTLY AMENDED) The kit of Claim 46, further comprising a computer ~~readable medium-~~ program comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

48. (PRESENTLY AMENDED) The kit of Claim 45, wherein said instructions comprise ~~a decision tree-~~ information to optimize perioperative care that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

49. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

50. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

51. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

52. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

53. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

54. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

55. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

56. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

57. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

58. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions

describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

59. (PREVIOUSLY ADDED) The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

60. (PREVIOUSLY ADDED) The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

61. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

62. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

63. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

64. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

65. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

66. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

67. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

68. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

69. (PRESENTLY CANCELLED)

70. (PRESENTLY CANCELLED)

71. (PRESENTLY AMENDED) A perioperative genomic profile kit having component parts ~~capable of being assembled for detecting~~ which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject and thereby providing a subject-specific clinical pathway for said subject, comprising a ~~decision tree~~ information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

## REMARKS

Claims 1-23 were filed in the original case. Claims 1-23 were cancelled and Claims 24-44 were added in a previous amendment. Claims 24-44 were cancelled and Claims 45-71

were added in a previous amendment. Claims 69 and 70 are cancelled in the present amendment. These cancellations are made without acquiescing to the Examiner's rejections, but are made to further prosecution and Applicant's business interests. Applicant reserves the right to prosecute Claims 69 and 70 (or similar claims) in the future. Claims 45-48 and 71 are presently amended. Therefore, Claims 45-68 and 71 are currently pending.

In the Office Action dated July 8, 2003 the Examiner has made three rejections. The currently pending rejections are:

- 1) Claims 46-48, 71 stand rejected under 35 U.S.C. 112, first paragraph;
- 2) Claims 45-68, 71 stand rejected under 35 U.S.C. 112, second paragraph; and
- 3) Claims 45, 48-68, 71 stand rejected under 35 U.S.C. 102(b).

Applicant believes that the pending Claims are fully supported, definite, and are not taught by the prior art. Therefore Claims 45-68, 71 should be passed into allowance.

## **REJECTIONS**

For clarity, the rejections at issue are set forth by number in the order they are herein addressed.

### **I. THE SPECIFICATION FULLY SUPPORTS THE CLAIMS**

The Examiner has rejected Claims 46-48, and 71 under 35 U.S.C. 112, first paragraph "... as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action 7/8/2003, page 3). Applicant respectfully disagrees. The Examiner argues: "The amendment fails to point to any support in the specification for the newly added language. However, the specification does not appear to describe or discuss "a computer readable medium" and a "decision tree". The concept of a computer readable medium" and a "decision tree" does not appear to be part of the originally filed invention. Therefore a computer readable medium" and a "decision "tree" constitutes new matter. Applicant is required to cancel the new matter in reply to this office action." (Office Action 7/8/2003, page 3.)

To the contrary, the Specification provides ample, specific and detailed support for the Claims. Several non-limiting examples are provided below:

“Assays for detection of polymorphisms or mutations fall into several categories, including, but not limited to direct sequencing assays, fragment polymorphism assays, hybridization assays, and ***computer based data analysis.***” (Specification, II. “Assays for Generating Genomic Profiles”, page 40. Emphasis added.)

“In some embodiments of the present invention, ***perioperative genomic profiles are generated using computer-based data analysis*** of a genetic information sample (e.g., stored nucleic acid sequence information). A sample is collected from a subject at anytime (e.g., at birth), sequence information is generated (e.g., through DNA sequencing), and ***the information is stored (e.g., as digital information on a portable chip).*** During the perioperative period, ***the subject's sequence information is scanned by a computer program*** for the pre-selected markers. A report (e.g., a perioperative genomic profile) is generated.” (Specification II.E., “Computer-Based Data Analysis”, page 49. Emphasis added.)

“In some embodiments of the present invention, ***the data is generated, processed, and/or managed using electronic communications systems*** (e.g., Internet-based methods). In some embodiments, ***a computer-based analysis program*** is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease).” (Specification, III. “Analysis and Delivery of Data”, page 50. Emphasis added.)

“Where the sample comprises previously determined genetic information (e.g., sequence information, SNP or mutation information, etc.), the information may be directly sent to the genomic profiling service by the subject (e.g., a information card containing the genetic information may be ***scanned by a computer and the data transmitted to a computer*** of the genomic profiling center using an electronic communication systems). Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical

or surgical procedure the subject will undergo.” (Specification, III. “Analysis and Delivery of Data”, pages 50-51. Emphasis added.)

“In some embodiments, the process of selecting markers, *performing detection assays*, and distributing data to subjects and clinicians is organized by an *integrated electronic (e.g., web-based) system.*” (Specification, “Detailed Description of the Invention”, page 30. Emphasis added.)

“The present invention contemplates *any method capable of receiving, processing, and transmitting the information to and from medical personal and subject.*” (Specification III., “Analysis and Delivery of Data”, page 50. Emphasis added.)

“In some preferred embodiments of the present invention, the information generated by perioperative *genomic profiling is distributed in a coordinated and automated fashion.*” (Specification III. “Analysis and Delivery of Data, page 49. Emphasis added.)

“The fate of the sample and genomic data is driven by the subject, who is given a menu (e.g. *electronically*) of choices. . . . For example, using an *electronic communication system*, the central facility can provide data to the clinician, the subject, or researchers. . . . In some embodiments, the subject may be able to directly access the data using the *electronic communication system.*” (Specification III. “Analysis and Delivery of Data, page 51. Emphasis added.)

“The data may be displayed to the clinician by any suitable method. For example, in some embodiments, the genomic profiling service generates a report that can be printed for the clinician (e.g., at the point of care) or *displayed to the clinician on a computer monitor.*” (Specification III., “Analysis and Delivery of Data”, page 51. Emphasis added.)

“The data generated by the assay may converted to a *genomic profile in a computer system* of the emergency vehicle or may be *transmitted to distant computer system for processing.*” (Specification III., “Analysis and Delivery of Data, page 51. Emphasis added.)

In order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar

claims) in the future, Applicant has amended Claims 46-48 and 71 to recite “computer program” and “information to optimize perioperative care”.

In view of the above, Applicant requests that these rejections be withdrawn.

## **II. THE CLAIMS ARE DEFINITE**

The Examiner has rejected Claims 45-68 and 71 under 35 U.S.C. 112, second paragraph “. . . as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.” (Office Action 7/8/2003, page 4.) The Examiner argues: “The response asserts that the claimed reagents provide agents for detecting the variant alleles using the range of different technologies described in the specification.” This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require that the reagents in fact detect the presence of the variant alleles. The claim could be amended to recite “reagents which detect . . .” to overcome the rejections.”

Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended Claims 45 and 71 to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively.

In view of the above, Applicant requests that these rejections be withdrawn.

## **III. THE CLAIMS ARE NOT ANTICIPATED**

The Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. For clarity and efficiency, because their defects as prior art are shared, and because the Examiner has cut and pasted from the Boehringer Mannheim text of the Office Action verbatim to the Perkin Elmer and Applied Biosystems text of the Office Action, the three references will be addressed together.

The text of 35 U.S.C. 102 quoted by the Examiner reads:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application in the United States.

(Office Action 7/8/2003, page 5).

Applicant respectfully asserts that the references cited by the Examiner glaringly fail to meet this standard of anticipation. To the contrary, the prior art references do **not** teach a perioperative genomic profile kit. The prior art references do **not** teach reagents which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . The prior art references do **not** teach instructions for using a kit for generating a perioperative genomic profile. The prior art references do **not** teach a kit having components that provide a subject-specific clinical pathway of medical intervention if used (see e.g., Claim 71).

The Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."<sup>1</sup>

Applicant respectfully submits that not one of the catalog references cited by the Examiner teach each and every element as set forth in the claims.

In view of the above, Applicant requests that these rejections be withdrawn.

### III. A. THE CLAIMS TEACH DETECTION OF SPECIFIC VARIANT ALLELES

In response to the 1/2/2003 Office Action, Applicant pointed out to the Examiner that: "None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention." (Response to Office

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<sup>1</sup> *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

Action, filed 5/11/2003, page 9). In the present Office Action the Examiner argues: "This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require detection of the variant alleles." (Office Action 7/8/2003, page 8).

Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended Claims 45 and 71 to recite "reagents which detect . . .", and "component parts which detect . . .", respectively. None of the cited references teach or suggest kits having reagents that detect the specific variant alleles.

In view of the above, Applicant requests that these rejections be withdrawn.

### **III. B. INSTRUCTIONS ARE FUNCTIONAL COMPONENTS OF THE CLAIMED KITS AND CANNOT BE IGNORED**

The Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one of the three prior art references recite "instructions for using said kit for generating said perioperative genomic profile for said subject." as recited in Claim 45, or the information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNA1S*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject, as recited in Claim 71. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring these elements. (Office Action 7/8/2003, page 8).

The Examiner argues that "In re Haller states that, in accordance with the patent statutes, an article or composition of matter, in order to be patentable, must not only be useful but must be new. *If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition regardless of the use for which it is intended.*" (Office Action 7/8/2003, page 9. Italics in original. Underline added.) In the immediately preceding Response to Office Action, Applicant pointed out

that the claimed instructions are novel, physical components dictating the manipulations of physical objects and activities which, as components of the claimed kits, implement a set of actions to accomplish a useful, concrete and tangible result. (Response to Office Action 5/11/2003, page 11). However, in the Office Action of 7/8/2003 the Examiner has conspicuously failed to respond to this statement of fact. Indeed, the Examiner concedes in the present Office Action that “The instructions are used to describe how the kit is intended to be used.” (Office Action 7/8/2003, page 9. Emphasis added).

Nevertheless, the Examiner continues to confuse *In re Haller*’s “the use for which it is intended” (i.e. the kit’s purpose), with “how the kit is intended to be used”, i.e. the claimed and patentable instructions for operation of the present invention that embody functional components interacting with other components of the claimed kits in novel modes of cooperation, thereby permitting the kit’s functionality to be realized.

In consideration of *In re Gulack*, the Examiner argues “in the case of *In re Gulack*, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself, which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed kit. The components of the kit remain fully functional absent the printed instructions for use.” (Office Action 7/8/2003, page 9). The Examiner’s mischaracterizations are erroneous, and unsupported by any evidence, affidavit or other authority. To the contrary, the claimed instructions of the present invention clearly result in a structural and manipulative differences (*In re Casey*) between the manufacturer’s catalogs cited by the Examiner as prior art, and the articles and compositions of the present claims. Rather than remaining fully functional, the useful, concrete and tangible aspects of the kits of the present claims are not maintained after removal of “printed instructions for use”.

Applicant submits herewith a Declaration of Morris Waxler, Ph.D. The Declaration explains that instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. For example, without instructions approved by the Food & Drug Administration, the *in vitro* diagnostic kit is not considered functional by the Food & Drug Administration.

The Examiner argues “The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually. Therefore, the kit is unpatentable over the prior art because they function equally effectively with or without instructions, and accordingly no functional relationship exists between the instructions for use and kit components.” (Office Action 7/8/2003, page 10).

In these assertions the Examiner makes numerous errors of both fact and law. First, the Examiner’s arguments are conclusory, and unsupported by any citation to relevant case law, the MPEP, an affidavit or other authority. Second, the Examiner once again confuses the “intended use which is recited on the instructions” with “printed instructions for use”. That is, the Examiner confuses the “intended use” of a kit (its purpose) with “how to use” the kit (i.e. its operation with the physical component instructions of the claims). Indeed the Examiner tacitly acknowledges the difference in distinguishing “intended use which is recited on the instructions”, from the body (how to) of the instructions. The claimed instructions of the present invention are not a “statement of intended use”. In Claims 45 - 68 they are physical component parts of the Claims. For example, a claim to “A system of doing X, comprising component Y” is anticipated by prior art that discloses component Y for purposes other than X (i.e., use X is a statement of use the does not impart patentable weight to the claim). However, a claim that recites “A system comprising component Y and component Z, wherein component Z is configured to permit component Y to find use in process X” is patentable if the prior art does not teach the use of component Y in process X, or does not teach the use of component Z that is configured to facilitate the use of Y for X. The present claims represent the latter rather than the former example.

Third, abundant examples are proffered in the Specification of instructions which both chemically and physically affect the chemical nature of the components of the kit (See Section I.B. “Criteria for Selection of Markers”, page 32, Section I.C. “Categories of Markers”, page 34, Experimental Example 1 “Perioperative Genomic Screening for

“Anesthesia Markers”, page 53, Experimental Example 2 “Generation of Genomic Profiles”, page 57.)

Fourth, the Examiner puts forward no relevant case law, MPEP citation, affidavit or other authority in which the legal test for a functional relationship rests on whether claims “physically or chemically affect the chemical nature of the components of the kit.” (Office Action 7/8/2003, page 10). This is a standard the Examiner has made up and does not comport with the law.

Fifth, whether or not “the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually)”, (Office Action 7/7/2003, page 10), has no legal bearing on patentability.

Sixth, the Examiner’s unsupported statement that “the kit is unpatentable over the prior art because they function equally effectively with or without the instructions” is clearly erroneous. The Examiner repeats the identical mistake a second time in consideration of *In re Miller* stating “no functional relationship exists between the instructions and the other elements of the kit because the components of the kit are capable of functioning without the printed matter.” (Office Action 7/8/2003, page 10) To the contrary, as evidenced by the Declaration of Morris Waxler, Ph.D., instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. Without instructions approved by the Food & Drug Administration, the *in vitro* diagnostic kit is not considered functional by the Food & Drug Administration, (i.e. the Food & Drug Administration recognizes the importance of the instructions to enable use of the reagents, and use of data obtained by use of the reagents in the hands of practitioners). To sustain the rejection, the Examiner must present evidence (not conclusory statements or guesses) as to the lack of a functional relationship between the claimed instructions and other components of the kits. Nor has the Examiner cited authority for the Examiner’s proposition that the test for a functional relationship is whether or not the components of the kit are capable of functioning without the printed matter. This is made-up law and does not reflect the actual law.

Finally, the Examiner argues that “Applicant’s arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a

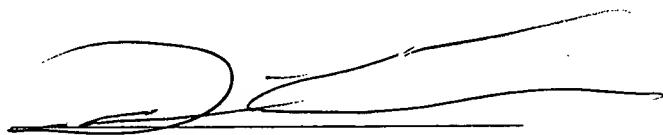
patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references." (Office Action 7/8/2003, page 11). To the contrary, in the Response to Office Action filed 5/11/2003 the Applicant expressly points out:

"None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention. None of the three references teaches categorical criteria for the selection of genes and variant alleles of the present invention. None of the three references teaches generation of a perioperative genomic profile." (Response to Office Action, 5/11/2003, page 9).

Applicant respectfully submits that the Boehringer Mannheim, Perkin Elmer, and Applied Biosystems catalog pages cited by the Examiner do not teach each and every element of the claims as required, and requests that the rejection under 35 USC §102 be withdrawn.

It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 9/8/03



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**PATENT**

Attorney Docket No. **HOGAN-06650**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of : Kirk Hogan  
Serial No.: 09/976,423 Group No.: 1634  
Filed: 10/21/2001 Examiner: J.A. Goldberg  
Entitled: Methods and Compositions for Perioperative Genomic Profiling

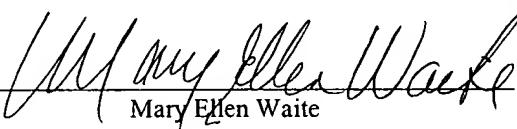
**DECLARATION OF MORRIS WAXLER, Ph.D.  
UNDER 37 CFR §1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(B)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 9-8-03

By:   
Mary Ellen Waite

Madam:

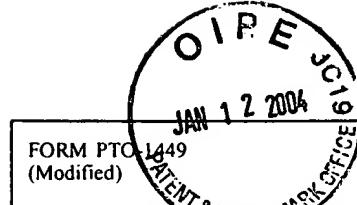
1. I, Morris Waxler, am a specialist in Food & Drug Administration regulatory affairs at the law firm of LaFollette, Godfrey & Kahn.
2. As a Branch Chief at the Center for Devices and Radiological Health of the Food & Drug Administration for 26 years, I am knowledgeable about Food & Drug Administration requirements for the manufacture and marketing of approved medical devices and diagnostic kits.
3. Instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to other components of the kit.
4. The function of an *in vitro* genetic diagnostic kit depends on the instructions to be approved by the Food & Drug Administration; without instructions the *in vitro* genetic diagnostic kit is not considered to be functional by the Food & Drug Administration.
5. Therefore an *in vitro* genetic diagnostic kit does not, and cannot, function equally effectively with or without instructions.

6. The functional relationship between an *in vitro* genetic diagnostic kit and its operation is critical such that component instructions must undergo rigorous Food & Drug Administration scrutiny before the kit may be manufactured or marketed in order to assure its safety, efficacy and reliability.

7. Without Food & Drug Administration approved instructions for its operation an *in vitro* genetic diagnostic kit cannot be manufactured or marketed.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: September 7, 2003      Signed: Morris Waxler  
Morris Waxler, Ph.D.



FORM PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No.: HOGAN-06650	Serial No.: 09/976,423
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use Several Sheets If Necessary)		Applicant: Kirk Hogan	
		Filing Date: 10/21/2001	Group Art Unit: 1634
(37 CFR § 1.98(b))			

## U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	Serial / Patent Number	Issue Date	Applicant / Patentee	Class	Subclass	Filing Date

## FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS

		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation
							Yes
							No

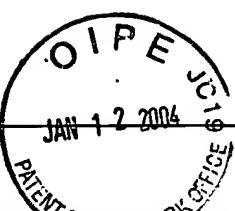
## OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)

1	Sweitzer B. (ed.), <i>Handbook of Preoperative Assessment and Management</i> , first edition, [2000], Lippincott, Williams and Wilkins, pgs 16-38
2	Erickson et al., <i>Anesthesia and Perioperative Complications</i> , second edition, [1999] pp. 741-751. Assessment of Anesthetic Risk
3	Baum et al., <i>Anesthesia for Genetic, Metabolic, and Dysmorphic Syndromes of Childhood</i> , first edition, [1999], Lippincott, Williams and Wilkins. This reference is a textbook and is not being supplied at this time but will be supplied at the Examiner's request..
4	Hardman et al., <i>Goodman &amp; Gilman's The Pharmacological Basis of Therapeutics</i> , ninth edition, [1996], McGraw-Hill. This reference is a textbook and is not being supplied at this time but will be supplied at the Examiner's request.
5	Bothner et al., Building a large scale perioperative anaesthesia outcome-tracking database: methodology, implementation, and experiences from one provider within the German quality project. <i>British Journal of Anaesthesia</i> 85(2): 271-80, 2000.
6	Douglas, Malignant hyperthermia persists though its profile changes. <i>Anesthesiology News</i> 25: 1 [1999]
7	Savarese et al., <i>Anesthesia</i> (RD, M., Ed.) pp 420, and 453, Churchill Livingstone, Philadelphia, PA. [2000]
8	Jacobs, <i>Progress in Anes</i> 7:39 [1998]. This reference is not being supplied at this time but will be supplied when available.
9	Schein et al., <i>NEJM</i> 342:168 [2000]
10	Roizen, <i>NEJM</i> 342:204 [2000]
11	Prows et al., Optimizing drug therapy based on genetic differences: implications for the clinical setting. <i>AACN Clinical Issues</i> 9(4), 499-512, 1998.
12	Kalow, <i>Pharmacological Reviews</i> 49:369 [1997] Pharmacogenetics in biological perspective.
13	Vesell, <i>Ann Int Med</i> 126:653 [1997] Therapeutic lessons from pharmacogenetics.
14	Ball et al., <i>Nature Biotechnology</i> 15:925 [1997] Pharmacogenetics and drug metabolism.
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16	Nebert, <i>Clin Genet</i> 56: 247 [1999] Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist?
17	Beaudet, <i>Am J Hum Genet</i> 64:1 [1999] 1998 ASHG presidential address.
18	Nebert, <i>Am J Hum Genet</i> 60:265 [1997] Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist?
19	Daly, <i>J Mol Med</i> 73:539 [1995] Molecular basis of polymorphic drug metabolism.
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21	Meyer, <i>PNAS</i> 91:1983 [1994] Pharmacogenetics: the slow, the rapid, and the ultrarapid.
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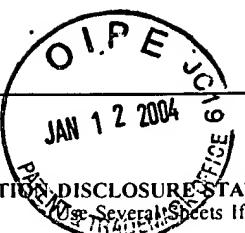
Examiner:	Date Considered:
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EXAMINER:	Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.
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FORM PTO-1449 (Modified)			U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No.: HOGAN-06650		Serial No.: 09/976,423	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use Several Sheets If Necessary)					Applicant: Kirk Hogan			
					Filing Date: 10/21/2001		Group Art Unit: 1634	
(37 CFR § 1.98(b))								
OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)								
	23	Marshall, <i>Nature Biotechnology</i> 15:954 [1997] Laying the foundations for personalized medicines						
	24	Time poll on genetic testing. [1999]						
	25	Licking, The Great Chip Derby. <i>Business Week</i> 10/25/99, 90, [1999]						
	26	Griffin <i>et al.</i> , <i>PNAS</i> , 96:6301 [1999] Direct genetic analysis by matrix-assisted laser desorption/ionization mass spectrometry						
	27	Yox, <i>Laboratory Medicine</i> 30: 456 [1999]						
	28	Gunderson <i>et al.</i> , <i>Genome Research</i> 8: 1142 [1998] Mutation detection by ligation to complete n-mer DNA arrays.						
	29	Harris <i>et al.</i> , <i>Nature Biotechnology</i> 18: 384 [2000] Injecting new ideas into microarray printing						
	30	Steemers <i>et al.</i> , <i>Nature Biotechnology</i> 18: 91 [2000] Screening unlabeled DNA targets with randomly ordered fiber-optic gene arrays.						
	31	Chen <i>et al.</i> , <i>Genome Research</i> 10: 549 [2000] A microsphere-based assay for multiplexed single nucleotide polymorphism analysis using single base chain extension.						
	32	Garvin <i>et al.</i> , <i>Nature Biotechnology</i> 18: 95 [2000] MALDI-TOF based mutation detection using tagged in vitro synthesized peptides.						
	33	Griffin <i>et al.</i> , <i>TIBTECH</i> 18: 77 [2000].						
	34	<i>Nature Genetics</i> 21:1 [1999]. "The Chipping Forecast". This reference is not being supplied at this time but will be supplied when available.						
	35	Fodor, <i>Science</i> 277: 393 [1997]						
	36	Gerhold <i>et al.</i> , DNA chips: promising toys have become powerful tools. <i>TIBS</i> 24: (May) [1999]						
	37	Blanchard <i>et al.</i> , <i>Nature Biotechnology</i> 17: 953 [1999] Cheap DNA arrays-it's not all smoke and mirrors.						
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<p style="text-align: center;">U.S. Patent and Trademark Office Information Disclosure Statement by Applicant (Use Several Sheets If Necessary) (37 CFR § 1.98(b))</p>		<p style="text-align: center;">U.S. Department of Commerce Patent and Trademark Office</p>		Attorney Docket No.: HOGAN-06650		Serial No.: 09/976,423		
				Applicant: Kirk Hogan				
				Filing Date: 10/21/2001		Group Art Unit: 1634		
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							Yes	No
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		Filing Date: 10/21/2001		Group Art Unit: 1634
(37 CFR § 1.98(b))				

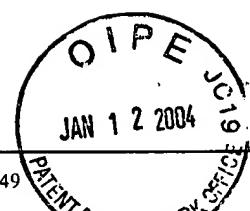
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Applicant: Kirk Hogan					
Filing Date: 10/21/2001				Group Art Unit: 1634	

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17	Leroyer <i>et al.</i> , <i>Thromb Haemost</i> [1998] Prevalence of the 2021- A allele of the prothrombin gene in venous thromboembolism patients.
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				Applicant: Kirk Hogan			
		Filing Date: 10/21/2001		Group Art Unit: 1634			
<b>U.S. PATENT DOCUMENTS</b>							
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		5,413,907	05/09/1995	Ronald G. Worton, <i>et al.</i>	435	6	09/21/1990
<b>FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS</b>							
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		WO 02/006536	01/24/2002	PCT Search Report			No
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**PATENT**  
Attorney Docket No. **HOGAN-06650**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

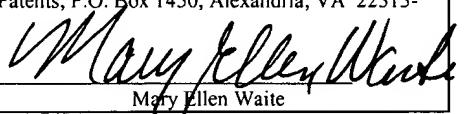
In re Application of: Kirk Hogan  
Serial No.: 09/976,423 Group No.: 1634  
Filed: 10/21/2001 Examiner: J.A. Goldberg  
Entitled: Methods and Compositions for Perioperative Genomic Profiling

**APPELLANTS' BRIEF**  
**APPEAL NO.:**

**CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. § 1.8(a)(1)(i)(B)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

DATED - JAN 8, 2004

By:   
Mary Ellen Waite

**Mail Stop Appeal Brief - Patents**  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Madam/Sir:

This Brief is in furtherance of the Notice of Appeal mailed herewith.

The fees required under SS 1.17(h) and any required Petition for Extension of time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

A request for a three month extension of time to extend the time of filing from October 8, 2003 to January 8, 2003 is attached.

**This Brief is transmitted in triplicate. [37 CFR SS 1.192(a).]**

This Brief contains these items under the following headings and in the order set forth below [37 CFR SS 1.192(c)]:

<b>I.</b>	<b>REAL PARTY IN INTEREST .....</b>	<b>3</b>
<b>II.</b>	<b>RELATED APPEALS AND INTERFERENCES .....</b>	<b>3</b>
<b>III.</b>	<b>STATUS OF CLAIMS .....</b>	<b>3</b>
<b>IV.</b>	<b>STATUS OF AMENDMENTS .....</b>	<b>3</b>
<b>V.</b>	<b>SUMMARY OF THE INVENTION .....</b>	<b>3</b>
<b>VI.</b>	<b>ISSUES .....</b>	<b>5</b>
<b>VII.</b>	<b>GROUPING OF CLAIMS .....</b>	<b>5</b>
<b>VIII.</b>	<b>ARGUMENT .....</b>	<b>8</b>

<b>IX. APENDIX A: CLAIMS INVOLVED IN THE APPEAL .....</b>	<b>29</b>
<b>X. APPENDIX B: AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION DATED JULY 8, 2003 .....</b>	<b>33</b>

**I. REAL PARTY IN INTEREST**

The real party in interest is the inventor of record, Kirk Hogan.

**II. RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences known to the Appellant or to the Appellant's legal representative.

**III. STATUS OF CLAIMS**

Claims 1-23 were filed in the original application. During prosecution of the application, Claims 1- 23 were cancelled and claims 24-44 were added in a previous amendment. Claims 24-44 were cancelled, and Claims 45-71 were added in the Amendment and Response to Office Action filed April 14, 2003. Claims 69 and 70 were withdrawn from consideration by the Examiner in the Final Office Action of July 8, 2003. Claims 45-68 and 71 have been rejected by the Examiner in the Final Office Action dated July 8, 2003. No other claims are pending. Therefore, Claims 45-68 and 71 are pending in this appeal. Appellant appeals the Final Office Action of July 8, 2003.

The Claims, as they now stand, are set forth in Appendix A.

**IV. STATUS OF THE AMENDMENTS**

With respect to the amendments of the Claims, Appellant's Amendment and Response of September 8, 2003 has not been entered by the Examiner. Appellant therefore submits as Appendix B the Amendment and Response to the Final Office

Action of July 8, 2003 (filed September 8, 2003) for review with this Appeal Brief, and requests that the amendment be entered herewith.

## **V. SUMMARY OF THE INVENTION**

The present invention relates to kits for perioperative genomic screening of patients for genetic markers indicative of responses to anesthesia, and to other surgical or operative treatments and procedures. In current clinical practice, there is no technology available that provides the information of the perioperative genomic profile kits of the present invention. In the past, screening tests of a patient's phenotype (*e.g.*, blood and urinalysis, EKG, and chest X-ray) were routinely performed prior to surgery. However, the present-day procedure for heritable disorders does not look at genetic information and is limited to asking a patient if they or their family members have had any previous difficulties with anesthesia or surgery. Sometimes, but not always, a physical exam is also performed. The use of laboratory phenotypic tests for patients prior to surgery has generally been reduced or eliminated. Reasons for elimination include the inaccuracy and lack of specificity of the phenotypic tests, the aggregate costs of heterogenous phenotypic screening panels, and uncertainty as to how to alter treatment course of action in response to results. Accordingly, contemporary anesthesiology and surgery textbooks emphasize that recent studies indicate a lack of benefit from routine phenotypic testing as a method of assessing patients preoperatively, and stress that cost-benefit strategies can only be justified when laboratory testing is reduced to that indicated by history-taking.

The perioperative genomic profile kits of the present invention stand in direct contrast to the panels of phenotypic tests currently available. In the present invention, genetic alleles are tested in ensemble according to selection categories and criteria taught by the present invention to construct a personalized perioperative genomic profile. The perioperative genomic profile kits of the present invention may be used, for example, to establish the subject's prognosis or odds of survival, to select the safest and most efficacious anesthetic regimen and surgical procedure, to determine the optimal level of post-surgical monitoring, and to begin life-saving intervention as soon as possible. The perioperative genomic profile kits of the present invention thereby solve many of the problems described above that have led practitioners away from preoperative phenotypic

testing. The perioperative genomic profile kits of the present invention are cost and time effective. Genomic markers are selected for inclusion in the kit, for example, by virtue of their analytical validity (accuracy, specificity, and predictive value), clinical validity and clinical utility. The perioperative genomic profile kits of the present invention thus allow, for example, for the individualization of treatment options for each subject undergoing a surgical procedure. In this fashion, the present invention provides a novel diagnostic tool currently unavailable in the surgical field, enabling solutions for problems that have no available alternatives. In the absence of any competing technology for quantifying subject's genetic contributors to perioperative risk, the present invention provides life- and cost-saving information to caregivers on an accelerated and amplified scale relative to current diagnostics.

## **VI. ISSUES**

There are three issues involved in the present appeal:

Issue 1 – Whether the Specification provides support for Claims 46-48 and 71 under 35 U.S.C. 112, first paragraph.

Issue 2 – Whether Claims 45-68, 71 are definite under 35 U.S.C. 112, second paragraph.

Issue 3 – Whether Claims 45, 48-68, and 71 are patentable under 35 U.S.C. 102(b) in view of:

- a) 1997 Boehringer Mannheim Biochemicals Catalog.
- b) 1996 Perkin Elmer, PCR Systems, Reagents & Consumables catalog.
- c) 1993 Applied Biosystems Catalog.

## **VII. GROUPING OF CLAIMS**

Each Claim stands alone. Each Claim has separate limitations and must be considered independently.

Independent Claim 45 specifies a kit for generating a perioperative genomic profile for a subject, comprising reagents capable of detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*,

*F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$ ; and instructions for using said kit for generating said perioperative genomic profile for said subject.*

Dependent Claim 46 specifies the kit of Claim 45, wherein the kit comprises a computer readable medium comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

Dependent Claim 47 specifies the kit of Claim 46, wherein the kit comprises a computer readable medium comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

Dependent Claim 48 specifies the kit of Claim 45, wherein the kit comprises instructions that comprise a decision tree that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

Dependent Claim 49 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

Dependent Claim 50 specifies the kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

Dependent Claim 51 specifies the kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

Dependent Claim 52 specifies the kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

Dependent Claim 53 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

Dependent Claim 54 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

Dependent Claim 55 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

Dependent Claim 56 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

Dependent Claim 57 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

Dependent Claim 58 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

Dependent Claim 59 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

Dependent Claim 60 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

Dependent Claim 61 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

Dependent Claim 62 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

Dependent Claim 63 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

Dependent Claim 64 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

Dependent Claim 65 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

Dependent Claim 66 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

Dependent Claim 67 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

Dependent Claim 68 specifies the kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

Independent Claim 71 specifies a perioperative genomic profile kit having component parts capable of being assembled for detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject, and thereby providing a subject-specific clinical pathway for said subject, comprising a decision tree that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

Because each of the independent claims have different limitations, they do not stand or fall together. Rather they must be evaluated separately.

## **VIII. ARGUMENT**

### **A. The Specification Fully Supports The Claims**

In the Final Office Action of July 8, 2003, the Examiner has rejected Claims 46-48, and 71 under 35 U.S.C. 112, first paragraph:

“Claims 46-48, 71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment fails to point to any support in the specification for the newly added language. However, the specification does not appear to describe or discuss “a computer readable medium” and a “decision tree”. The concept of “a computer readable medium” and a “decision tree” does not appear to be part of the originally filed invention. Therefore “a computer readable medium” and a “decision “tree” constitutes new matter. Applicant is required to cancel the new matter in reply to this office action.” (Final Office Action July 8, 2003, page 3.) (Emphasis added.)

In the Amendment and Response to Final Office Action Dated July 8, 2003 Appellant respectfully disagreed with the Examiner. To the contrary, the Specification provides ample, specific and detailed support for the Claims. Several non-limiting examples directly quoted from the Specification were provided to the Examiner (Amendment and Response to Final Office Action Dated July 8, 2003, pages 7-9):

“Assays for detection of polymorphisms or mutations fall into several categories, including, but not limited to direct sequencing assays, fragment polymorphism assays, hybridization assays, and computer based data analysis.” (Specification, II. “Assays for Generating Genomic Profiles”, page 40. Emphasis added.)

“In some embodiments of the present invention, perioperative genomic profiles are generated using computer-based data analysis of a genetic information sample (e.g., stored nucleic acid sequence information). A sample is collected from a subject at anytime (e.g., at birth), sequence information is generated (e.g., through DNA sequencing), and the information is stored (e.g., as digital information on a portable chip). During the perioperative period, the subject's sequence information is scanned by a computer program for the pre-selected markers. A report (e.g., a perioperative genomic profile) is generated.” (Specification II.E., “Computer-Based Data Analysis”, page 49. Emphasis added.)

“In some embodiments of the present invention, the data is generated, processed, and/or managed using electronic communications systems (e.g., Internet-based methods). In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease).” (Specification, III. “Analysis and Delivery of Data”, page 50. Emphasis added.)

“Where the sample comprises previously determined genetic information (e.g., sequence information, SNP or mutation information, etc.), the information may be directly sent to the genomic profiling service by the subject (e.g., a information card containing the genetic information may be scanned by a computer and the data transmitted to a computer of the genomic profiling center using an electronic communication systems). Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo.” (Specification, III. “Analysis and Delivery of Data”, pages 50-51. Emphasis added.)

“In some embodiments, the process of selecting markers, performing detection assays, and distributing data to subjects and clinicians is organized by an integrated electronic (e.g., web-based) system.” (Specification, “Detailed Description of the Invention”, page 30. Emphasis added.)

“The present invention contemplates any method capable of receiving, processing, and transmitting the information to and from medical personal and subject.” (Specification III., “Analysis and Delivery of Data”, page 50. Emphasis added.)

“In some preferred embodiments of the present invention, the information generated by perioperative genomic profiling is distributed in a coordinated and automated fashion.” (Specification III. “Analysis and Delivery of Data, page 49. Emphasis added.)

“The fate of the sample and genomic data is driven by the subject, who is given a menu (e.g. electronically) of choices. . . For example, using an electronic communication system, the central facility can provide data to the clinician, the subject,

or researchers. . . . In some embodiments, the subject may be able to directly access the data using the electronic communication system.” (Specification III. “Analysis and Delivery of Data, page 51. Emphasis added.)

“The data may be displayed to the clinician by any suitable method. For example, in some embodiments, the genomic profiling service generates a report that can be printed for the clinician (e.g., at the point of care) or displayed to the clinician on a computer monitor.” (Specification III., “Analysis and Delivery of Data”, page 51. Emphasis added.)

“The data generated by the assay may converted to a genomic profile in a computer system of the emergency vehicle or may be transmitted to distant computer system for processing.” (Specification III., “Analysis and Delivery of Data, page 51. Emphasis added.)

In the Advisory Action of October 16, 2003 the Examiner has completely ignored this abundant, specific and objective evidence of support in the Specification for Claims 45-48, and 71 and has failed to address or enter Appellant’s claim amendments that sought to utilize language in the claims more directly aligned to the language of the specification (although Appellant believes that the claim language of the both the original and amendment claims are properly supported by the specification). In these amendments, which Appellant requests be entered with this Appeal, Claims 46-48 and 71 are amended to recite “computer program” and “information to optimize perioperative care.”(Amendment and Response to Final Office Action Dated July 8, 2003, page 9.).

Both the original claims and the amended claims are clearly supported in the specification. The Examiner’s failure to address Appellant’s evidence and argument is error. Appellant is entitled to have its arguments considered; yet no such consideration was given. For the reasons discussed in Section C, below, consideration of the argument, with or without entry of the amendment, results in at least claims 46 and 47 being allowed. Thus, failure to consider the arguments (and/or amendments) prejudices Appellant.

## **B. The Claims are Definite**

In the Final Office Action of July 8, 2003 the Examiner has rejected Claims 45-68 and 71 under 35 U.S.C. 112, second paragraph:

“Claims 45-68, 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.”

“The response asserts that the claimed reagents provide agents for detecting the variant alleles using the range of different technologies described in the specification.” This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require that the reagents in fact detect the presence of the variant alleles. The claim could be amended to recite “reagents which detect . . . “ to overcome the rejections.” (Page 4.) (Emphasis added.)

In the Amendment and Response to Final Office Action Dated July 8, 2003, Appellant respectfully disagreed with the Examiner. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Appellant amended Claims 45 and 71 to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively as requested by the Examiner.

In the Advisory Action of October 16, 2003, the Examiner did not address the amendments which the Examiner had suggested with particularity in the Final Office Action of July 8, 2003. In view of the above, Appellant requests the Board withdraw this rejection and enter the amendments, as there appears to be no issue here when the amendments are entered.

#### **C. The Examiner has Improperly Failed to Enter Appellant’s Amendments**

Claims 46 and 47 are only rejected under the 112 grounds discussed in Sections A and B, above. They are not rejected under the prior art. Appellants amendments filed with the Response to the Final Office Action address the Examiners concerns: in one case changing the terminology as suggested by the Examiner to overcome an indefiniteness rejection and in the other case substituting the term “computer

program" for "computer readable medium" to overcome a new matter rejection. That these amendments overcome the rejections is unquestionable for the reasons discussed in Sections A and B, above. As these are the only bases for rejection of Claim 46 and 47, the amendments unquestionably place the claims in position for allowance. Therefore, amendments should have been entered and the claims should have been allowed. The only basis in the Advisory Action cited by the Examiner for failing to enter the amendments is the checked box, "[the amendments] raise new issues that would require further consideration and/or search (see NOTE below)", with the corresponding note simply saying that the arguments are moot—providing no reasons why this is the case. The Examiner has not pointed to any basis why new searches would be required (indeed - they should not be since the claims that were pending prior to the Final rejection contained computer elements, and the Examiner was aware of extensive prior art related to the invention from this application and parent application #09/613,887; a copy of form 1449 is attached hereto at Tab C), or why further consideration is required (the claims unquestionably find support in the specification, clearly rendering the new matter rejection moot without further consideration). Had the amendments been entered, the claims would be allowed and Sections A, B, and C of the Appeal would be unnecessary.

#### **D. The Cited References do not Anticipate the Claims**

In the Final Office Action of July 8, 2003, the Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. For clarity and efficiency, because their defects as prior art are shared, and because the Examiner has cut and pasted verbatim from the Boehringer Mannheim text of the Final Office Action of July 8, 2003 to the Perkin Elmer and Applied Biosystems texts (without even changing "Boehringer Mannheim" to "Perkin Elmer" (page 12) or "Applied Biosystems" (page 17)), the three references will be addressed together.

The text of 35 U.S.C. 102 quoted by the Examiner reads:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or

in public use or on sale in this country, more than one year prior to the date of application in the United States.

(Final Office Action July 8, 2003, page 5).

Appellant respectfully asserts that the references cited by the Examiner strikingly fail to meet this standard of anticipation. To the contrary, the catalog pages do not teach a perioperative genomic profile kit. The catalog pages do not teach reagents which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . The catalog pages do not teach instructions for using a kit for generating a perioperative genomic profile. The catalog pages do not teach computer programs or information to optimize perioperative care. The prior art references do not teach a kit having components that provide a subject-specific clinical pathway of medical intervention if used.

In the Amendment and Response to Final Office Action Dated July 8, 2003, Appellant reminded the Examiner that the Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."<sup>1</sup>

Appellant respectfully submits that not one of the catalog references cited by the Examiner teach each and every element as set forth in the claims.

**1. The Claims Require Detection of Specific Variant Alleles - The Examiner's Cited Catalog Pages Do Not Teach this Element**

In the Appellant's Amendment and Response to Office Action Dated January 21, 2003 (filed April 14, 2003), Appellant pointed out to the Examiner that:

"None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two

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<sup>1</sup> *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

or more genes from the group of genes of the present invention.” (Amendment and Response to Office Action of January 21, 2003, filed April 14, 2003, page 9).

In the Final Office Action of July 8, 2003 the Examiner argues:

“This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require detection of the variant alleles.” (Final Office Action July 8, 2003, page 8).

Appellant respectfully disagrees. To the contrary, the catalog pages cited by the Examiner have no teaching or suggestion to use variant alleles of two or more of the claimed genes. Thus, none of the cited references teach or suggest kits having reagents capable of detecting the specific variant alleles as recited in the claims. Hence, the Examiner has not responded to the main point of Appellant’s rebuttal.

However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Appellant had amended Claims 45 and 71 as suggested by the Examiner to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively.

In the Examiner’s Advisory Action of October 16, 2003, the Examiner fails to consider these amendments that the Examiner suggested with particularity. In view of the above, Appellant requests the Board withdraw this rejection and enter the amendments or otherwise pass the original claims to allowance as the prior art fails to teach the elements of either the original claims or the amended claims.

## **2. Instructions are Functional Components of the Claimed Kits and Cannot be Ignored**

In the Final Office Action of July 8, 2003 the Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one

of the three prior art references recite the limitation “instructions for using said kit for generating said perioperative genomic profile for said subject.” as recited in Claim 45. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring this element. (Final Office Action July 8, page 8).

**a. The Examiner’s Rejection of Instructions as Functional Components of the Claimed Kits is Procedurally Defective**

The Examiner has never argued in the Office Action of December 2, 2002, in the Office Action of January 21, 2003, in the Final Office Action of July 8, 2003, or in the Advisory Action of October 16, 2003 that the cited catalog references teach instructions for the operation of a perioperative genomic profiling kit. Hence, the Examiner’s argument that the cited art references anticipate the present invention under 35 U.S.C, 102(b) is procedurally defective, and must be withdrawn.

Rather, the Examiner argues whether instructions for generating a perioperative genomic profile are a legitimate claim element, not whether instructions for the operation of the kit are anticipated by the Examiner’s references. (Final Office Action of July 8, 2003, pages 9-11.) To the contrary, if instructions are a legitimate claim element, then there is no question that the prior art cited by the Examiner fails to teach or suggest the limitation. Nor has the Examiner asserted otherwise. Therefore, the claims are allowable if the instructions are an element of the Claims. Incontrovertibly they are.

**b. The Examiner Confuses Instructions for the Operation of a Kit with a “Statement of Intended Use” and Has Failed to Properly Respond to Appellant’s Response**

In the Advisory Action of October 16, 2003 the Examiner argues:

“The response asserts that the intended use which is recited on the instructions with printed instructions for use. (sic) This argument has been thoroughly addressed in the final rejection.” (Page 3).

Appellant submits that it is impossible to know what the Examiner means in the first sentence since the Examiner has failed to proofread the sentence. Appellant therefore assumes that the Examiner is reiterating the same arguments as those to be found in the Final Office Action of July 8, 2003 (pages 9-11) in which the Examiner confuses instructions for the operation of a kit with a statement of intended use. For example, the Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). (Office Action 7/8/2003, page 10).

If this is in fact what the Examiner has meant in the Advisory Action of October 16, 2003, then the Appellant’s argument has not been thoroughly addressed in the Appellant’s Amendment and Response to the Office Action of January 21, 2003, or even addressed at all in the Appellant’s Amendment and Response to Final Office Action Dated July 8, 2003.

For example, in the Final Office Action of July 8, 2003, the Examiner argues:

“*In re Haller* states that, in accordance with the patent statutes, an article or composition of matter, in order to be patentable, must not only be useful but must be new. *If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition regardless of the use for which it is intended.*” (Final Office Action July 8, 2003, page 9. Italics in original. Underline added.)

However, *In re Haller* is of no relevance to rejection of the present invention. Instructions are not a “statement of intended use”, nor are instructions “mere re-labelling” (*In re Haller*, 403). In citing *In re Haller*, the Examiner mistakenly confuses operational

kit instructions with “an admittedly old compound, labelled for a new use as an insecticide”, (*id* at 403), while *In re Haller* itself does not. Indeed, the term “instructions” and “kit” fail to appear anywhere in the text of *In re Haller*.

In the Amendment and Response to Office Action of January 21, 2003, Appellant pointed out that the claimed instructions are novel, physical components dictating the manipulations of physical objects and activities which, as components of the claimed kits, implement a set of actions to accomplish a useful, concrete and tangible result. (Page 11.) Under some embodiments of the presently invention, instructions that direct, for example, a treatment course of action utilize physically organized data structures for two or more assays, which are not fixed or determinate beforehand. A patient’s preferred clinical pathway cannot properly be executed in advance absent the results of the assay as instructed. Instructions that cause and direct a particular treatment course of action utilize results from two or more genotypes. A combination of markers may well instruct one course of action rather than another.

In the Final Office Action of July 8, 2003, and in the Advisory Action of October 16, 2003, the Examiner has conspicuously failed to respond to these factual assertions. Indeed, the Examiner concedes in the Final Office Action of July 8, 2003 that:

“The instructions are used to describe how the kit is intended to be used.”

(Final Office Action of July 8, 2003, page 9. Emphasis added).

Nevertheless, in the Final Office Action of July 8, 2003 and the Advisory Action of October 16, 2003 the Examiner continues to confuse *In re Haller*’s “the use for which it is intended” (i.e. a statement of the kit’s purpose), with “how the kit is intended to be used”, i.e. the claimed and patentable instructions for operation of the present invention that embody functional components, interacting with other components of the claimed kits, in novel modes of cooperation, thereby permitting the kit’s functionality to be realized. (Amendment and Response to Office Action January 21, 2003, page 11.) In the Amendment and Response to Final Office Action of July 8, 2003 Appellant explained to the Examiner that the instructions of Claims 45 - 68 are physical component parts of the Claims (page 13). For example, a claim to “A system of doing X, comprising component

Y" is anticipated by prior art that discloses component Y for purposes other than X (i.e., use X is a statement of use the does not impart patentable weight to the claim). However, a claim that recites "A system comprising component Y and component Z, wherein component Z is configured to permit component Y to find use in process X" is patentable if the prior art does not teach the use of component Y in process X, or does not teach the use of component Z that is configured to facilitate the use of Y for X. The present claims represent the latter rather than the former example.

Contrary to thoroughly addressing these facts, the Examiner has been mute in response. In view of the above, Appellant requests that the Board direct the Examiner to respond to the Appellant's rebuttal, or to withdraw the rejections.

**c. The Examiner has Improperly Applied the Law of *In re Gulack*, Which Stands for the Patentability of the Present Invention**

In the Advisory Action of October 16, 2003 the Examiner argues:

"Fourth, the response again asserts there is no case law or MPEP citation which is relevant such that the examiner has made up and does not comport with the law. Applicant is respectfully requested to read *in re Gulack*."

*In re Gulack* was provided by the Appellant to the Examiner in support of the assertion that "... printed matter, in an article of manufacture claim, *can* be given "patentable weight."<sup>2</sup> (Original emphasis.) The CAFC in *In re Levin* holds:

"The only requirement that 35 U.S.C. §101 imposes as set forth in *In re Miller* is that a new and unobvious functional relationship must exist between the claimed combination of printed matter and other claimed elements. 418 F.2d at 1396, 164 U.W.P.Q. (BNA) at 49. For instance, as we have stated in *In re Gulack*, "the critical question is whether there exists any new and unobvious functional

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<sup>2</sup> *In re Miller* 57 C.C.P.A. 809; 418 F.2d 1392.

relationship between the printed matter and the substrate.” 703 F.2d at 1386, 217 U.S.P.Q. (BNA) at 404.<sup>3</sup>

Because novel, unobvious functional relationships clearly exist between the claimed instructions and substrate kits, the present invention easily surmounts the requirements of the *In re Gulack* test. An instruction is “An authoritative direction to be obeyed; an order”; instructions are “Detailed directions on procedure.” (The American Heritage Dictionary 3<sup>rd</sup> Edition, 1993). Clearly instructions do not “merely represent a statement of intended use” as the Examiner mistakenly alleges (Office Action of January 21, 2003, page 3). Hence, *In re Gulack* stands for exactly the opposite of the Examiner’s conclusory and unsupported assertion.

In the Final Office Action of July 8, 2003 the Examiner argues:

“However, in the case of *In re Gulack*, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself, which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed kit. The components of the kit remain fully functional absent the printed instructions for use.” (Final Office Action July 8, 2003, page 9)

The Examiner’s mischaracterizations of the present invention’s Claims are erroneous, and unsupported by any evidence, affidavit or other authority. To the contrary, the claimed instructions of the present invention clearly result in a structural and manipulative differences (*In re Casey*) between the manufacturer’s catalogs cited by the Examiner as prior art, and the articles and compositions of the present claims. Rather than remaining fully functional, the useful, concrete and tangible aspects of the kits of the present claims are not maintained after removal of “printed instructions for use”. In turn, the Examiner’s argument, raised for the first time in the Final Office Action of July 8, 2003, that “The components of the kit remain fully functional absent the printed

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<sup>3</sup> *In re Levin*, 107 F.3d 30 (Fed. Cir. 1997).

instructions for use.” represents a new and rebuttable ground of rejection that are unsupported by fact or evidence.

**d. The Examiner Improperly Fails to Consider the Declaration of Dr. Morris Waxler**

In the Advisory Action of October 16, 2003 the Examiner argues regarding the Declaration of Morris Waxler, Ph.D.:

“Affidavits and declarations submitted under 37 C.F.R. 1.132 and other evidence traversing rejections are considered timely if submitted:

...

(3) after final rejection and submitted

(i.) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection,”

(Advisory Action October 16, 2003, page 1).

The Examiner then makes the conclusory and unsupported assertion that the Declaration submitted with the September 8, 2003 Amendment and Response to Final Office Action “does not address a new ground of rejection.”

The Examiner is in error. In the Final Office Action of July 8, 2003 the Examiner makes the following new ground of rejection:

“The components of the kit remain fully functional absent printed instructions for use.” (Final Office Action July 8, 2003, page 9).

This ground for rejection is nowhere to be found in the Office Action of January 21, 2003. Therefore, the Examiner’s assertion is incontestably a new ground of rejection in the Final Office Action of July 8, 2003. Because the Examiner has made this new and baseless ground of rejection in the Final Office Action of July 8, 2003, under 37 C.F.R. 1.132(3)(i) Appellant is entitled to provide rebuttal evidence to the Examiner’s unsupported and conclusory speculation.

e. **Dr. Morris Waxler's Declaration Is Evidence of a Functional Relationship Between Operational Instructions and the Perioperative Genomic Profile Kits of the Present Invention which the Examiner has not Refuted**

The Examiner's unsupported statement that "the kit is unpatentable over the prior art because they function equally effectively with or without the instructions" is clearly erroneous. The Examiner repeats the identical mistake a second time in consideration of *In re Miller* stating:

"no functional relationship exists between the instructions and the other elements of the kit because the components of the kit are capable of functioning without the printed matter." (Final Office Action of July 8, 2003, page 10)

And:

"the kit is unpatentable over the prior art because they function equally effectively with or without instructions, and accordingly no functional relationship exists between the instructions for use and kit components." (Final Office Action of July 8, 2003 page 10).

To the contrary, as evidenced by the Declaration of Morris Waxler, Ph.D., instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. Dr. Waxler explains:

"The function of an *in vitro* genetic diagnostic kit depends on the instructions to be approved by the Food & Drug Administration; without instructions the *in vitro* genetic diagnostic kit is not considered to be functional by the Food & Drug Administration."

"an *in vitro* genetic diagnostic kit does not, and cannot, function equally effectively with or without instructions."

“The functional relationship between an *in vitro* genetic diagnostic kit and its operation is critical such that component instructions must undergo rigorous Food & Drug Administration scrutiny before the kit may be manufactured or marketed in order to assure its safety, efficacy and reliability.”

“Without Food & Drug Administration approved instructions for its operation an *in vitro* genetic diagnostic kit cannot be manufactured or marketed.”  
(Declaration of Morris Waxler, Ph.D. under 37 CFR §1.132, page 1)

Contrary to the Examiner’s unsupported assertions, the Food & Drug Administration recognizes the importance of the instructions to enable use of the reagents, and use of data obtained by use of the reagents in the hands of practitioners.

To sustain the rejection, the Examiner must present evidence (not conclusory statements or guesses) as to the lack of a functional relationship between the claimed instructions and other components of the kits. The Examiner’s rejection is not evidence. The Declaration is objective factual evidence. Examiner’s failure to consider the Declaration is defective as a matter of law. The Examiner is not in possession of countervailing factual evidence. Nor has the Examiner cited authority for the Examiner’s proposition that the test for a functional relationship is whether or not the components of the kit are capable of functioning without the printed matter. This is made-up law and does not reflect the actual law.

Therefore, Appellant requests the Board to withdraw the rejections or to direct the Examiner to consider the Declaration of Morris Waxler, PhD, and to withdraw the rejections.

**f. The Examiner’s “Physically or Chemically Affect the Chemical Nature” Standard is not the Law under 35 U.S.C. 102(b)**

In the Advisory Action of October 16, 2003 the Examiner argues:

“The third reason the response traverses is that the instructions both chemically and physically affect the chemical nature of the components of the kit. The final rejection has thoroughly responded to this arguments”. (Page 3.)

To the contrary the Examiner hasn't responded to the Appellant thoroughly or at all.

In the Final Office Action of July 8, 2003 the Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). (Final Office Action July 8, 2003, page 10).

In this assertion the Examiner makes numerous errors of both fact and law. First, the Examiner's arguments are conclusory, and unsupported by any citation to relevant case law, the MPEP, an affidavit, or other authority. Second, the Examiner confuses the “intended use which is recited on the instructions” with “printed instructions for use” Indeed the Examiner tacitly acknowledges the difference in distinguishing “intended use which is recited on the instructions”, from the body (how to) of the instructions. The claimed instructions of the present invention are not a “statement of intended use” (see above). Third, abundant examples are proffered in the Specification of instructions which both chemically and physically affect the chemical nature of the components of the kit (See Section I.B. “Criteria for Selection of Markers”, page 32, Section I.C. “Categories of Markers”, page 34, Experimental Example 1 “Perioperative Genomic Screening for Anesthesia Markers”, page 53, Experimental Example 2 “Generation of Genomic Profiles”, page 57).

Fourth, the Examiner puts forward no relevant case law, MPEP citation, affidavit or other authority in which the legal test for a functional relationship rests on whether operational instructions “physically or chemically affect the chemical nature of the components of the kit.” (Final Office Action July 8, 2003, page 10). This is a standard the Examiner has made up and does not comport with the law.

g. **The Examiner’s “Use for Other Purposes” Standard is not the law under 35 U.S.C. 102(b)**

The Examiner argues:

“The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). Therefore the kit is unpatentable over the prior art . . .”  
(Office Action 7/8/2003, page 10).

Appellant asserts that whether or not “the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually)” has no legal bearing on patentability. To reach this peculiar and erroneous standard the Examiner has misinterpreted the Examiner’s own quoted law. For example, the Examiner argues:

“Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152, USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938 136 USPQ 458, 459, (CCPA 1963). (Final Office Action of July 8, 2003, page 9)

Nothing in the cited case law elucidates a standard that “use for other purposes” defines improper functional language. As detailed above, instructions for the operation of a genomic profiling kit are not a “statement (or recitation) of intended use” as mischaracterized by the Examiner, regardless of whether the reagents have additional potential uses. In the Advisory Action of October 16, 2003, the Examiner argues:

”The response argues that the claims are not anticipated. The response asserts the examiners arguments are conclusory and unsupported by case law or the MPEP. The rejection of record cites both MPEP and case law on number of occasions (see pages 9-11, for example).” (Page 3.)

Appellant submits that the Examiner has misinterpreted the proper standard established by the MPEP and case law which - when considered - stands for the patentability of the present invention. Moreover, the Examiner impermissibly attempts to create a new legal standard, (i.e. whether “the components of the kit can be used by the skilled artisan for other purposes (wholly or individually)”). In view of the above, Appellant requests that the Board withdraw this rejection.

**h. The Examiner has Improperly Ignored Appellant’s Arguments Showing Distinguishing Features Between the Claims and the Prior Art**

In the Final Office Action of July 8, 2003 the Examiner argues:

“Applicant’s arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.” (page 11).

To the contrary, in the Amendment and Response to Office Action Dated January 21, 2003 (filed April 14, 2003), the Appellant expressly and specifically responded to the Examiner:

“None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention. None of the three references teaches categorical criteria for the selection of genes and variant alleles

of the present invention. None of the three references teaches generation of a perioperative genomic profile.” (page 9).

Although these facts were pointed out to the Examiner in the Amendment and Response to Final Office Action Dated July 8, 2003 (filed September 8, 2003), the Examiner made no response in the Advisory Action of October 16, 2003. Appellant therefore requests that the Board withdraw this rejection under 35 USC §102(b) or direct the Examiner to properly consider Appellant’s arguments.

For the numerous reasons cited above, the Examiner has improperly failed to consider the claim element of “instructions” in the claims. There is no dispute that this element is not found in the prior art. Because this element must be considered, for at least the reasons recited above, the rejections must be withdrawn and the claims passed to allowance.

### **3. The Examiner has Not Read Claim 71**

The Examiner has failed to properly address the patentability of Claim 71. It appears that the Examiner has misread the claim. In particular, the Examiner rejects Claim 71 on grounds that are irrelevant to the claim. Because the Examiner has failed to properly address the claim, Claim 71 must either be passed to allowance or a non-final office action must be issued on Claim 71.

In the Final Office Action of July 8, 2003 the Examiner has rejected Claim 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one of the three prior art references recites a perioperative genomic profile kit having component parts which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . Not one of the three prior art references recites a genomic profiling kit comprising information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention

for said subject, as recited in Claim 71. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring the absence of these limitations in the catalogs cited as prior art references. (Final Office Action July 8, page 8).

Importantly, although the Examiner groups rejection of Claim 71 with rejections of Claims 45, and 48-68 in consideration of “arguments directed to instructions” (Final Office Action of July 8, 2003, page 8), instructions for the operation of perioperative genomic profiling kits are not an element of Claim 71. In lumping Claim 71 into the other rejections, the claim elements unique to Claim 71 have been entirely ignored. Thus, the subject matter of Claim 71 has never been addressed by the Examiner. Because the Examiner has failed to properly address the claim, Claim 71 must either be passed to allowance or a non-final office action must be issued on Claim 71.

#### **E. CONCLUSION**

For the foregoing reasons, it is submitted that the Examiner’s rejection of Claims 45-68, and 71 was erroneous, and reversal of the rejection is respectfully requested. The Appellant requests that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Examiner.

Dated: 1/8/04



David A. Casimir  
Registration No. 42,395

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## **APPENDIX A: CLAIMS INVOLVED IN THE APPEAL**

45. A kit for generating a perioperative genomic profile for a subject, comprising:

- a) reagents capable of detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* ; and
- b) instructions for using said kit for generating said perioperative genomic profile for said subject.

46. The kit of Claim 45, further comprising a computer readable medium comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

47. The kit of Claim 46, further comprising a computer readable medium comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

48. The kit of Claim 45, wherein said instructions comprise a decision tree that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*,

*TNF $\alpha$*  and *TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

49. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

50. The kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

51. The kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

52. The kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

53. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

54. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

55. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

56. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

57. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

58. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

59. The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

60. The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

61. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

62. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

63. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

64. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

65. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

66. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

67. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

68. The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

71. A perioperative genomic profile kit having component parts capable of being assembled for detecting the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject and thereby providing a subject-specific clinical pathway for said subject, comprising a decision tree that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

**PATENT**Attorney Docket No. **HOGAN-06650****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Kirk Hogan  
Serial No.: 09/976,423 Group No.: 1634  
Filed: 10/21/2001 Examiner: J.A. Goldberg  
Entitled: Methods and Compositions for Perioperative Genomic Profiling

**AMENDMENT AND RESPONSE TO FINAL OFFICE  
ACTION DATED JULY 8, 2003**

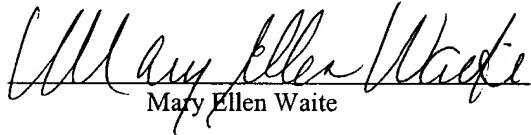
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(B)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 9-8-03

By:

  
Mary Ellen Waite

Madam:

The following communication is responsive to the Final Office Action mailed July 8, 2003, due on or before September 8, 2002 to provoke an Advisory Action. The Applicant respectfully requests reconsideration of the Application in view of the following amendment and remarks.

**I. IN THE CLAIMS:**

Claims 1 - 44 (previously cancelled).

45. (PRESENTLY AMENDED) A kit for generating a perioperative genomic profile for a subject, comprising:

- a) reagents ~~capable of detecting~~ which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* ; and
- b) instructions for using said kit for generating said perioperative genomic profile for said subject.

46. (PRESENTLY AMENDED) The kit of Claim 45, further comprising a computer ~~readable medium~~ program comprising instructions for using said kit for generating said perioperative genomic profile for said subject.

47. (PRESENTLY AMENDED) The kit of Claim 46, further comprising a computer ~~readable medium~~ program comprising computer instructions which direct a processor to analyze data derived from use of said reagents.

48. (PRESENTLY AMENDED) The kit of Claim 45, wherein said instructions comprise ~~a decision tree~~ information to optimize perioperative care that, based on at least the presence of variant alleles of two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF $\alpha$  and TNF $\beta$* , directs a user to a specific perioperative clinical pathway for said subject.

49. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate general anesthesia treatment course of action.

50. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is an inhalational treatment course of action.

51. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is an intravenous treatment course of action.

52. (PREVIOUSLY ADDED) The kit of Claim 49, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

53. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate regional anesthesia treatment course of action.

54. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate combined regional and general treatment course of action.

55. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate non-invasive surgery treatment course of action.

56. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate invasive surgery treatment course of action.

57. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate anesthesia treatment course of action during a medical procedure.

58. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions

describe how said perioperative genomic profile is analyzed in selecting appropriate dosages of analgesic compounds.

59. (PREVIOUSLY ADDED) The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to increase the dosage of analgesic compounds metabolized by CYP2D6.

60. (PREVIOUSLY ADDED) The kit of Claim 54, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease the dosage of analgesic compounds metabolized by CYP2D6.

61. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate prophylaxis for thrombosis.

62. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to increase prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

63. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed to decrease prophylaxis for thrombosis mediated by variant alleles of *F5*, *F2*, *MTHFR*, *MTR*, *MTRR*, and *CBS*.

64. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting appropriate monitoring procedures.

65. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting pre-operative phenotypic tests and consultations.

66. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after an anesthesia treatment course of action.

67. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in providing a prognosis after a surgical treatment course of action.

68. (PREVIOUSLY ADDED) The kit of Claim 45, wherein said instructions describe how said perioperative genomic profile is analyzed in selecting an appropriate post-operative treatment course of action.

69. (PRESENTLY CANCELLED)

70. (PRESENTLY CANCELLED)

71. (PRESENTLY AMENDED) A perioperative genomic profile kit having component parts ~~capable of being assembled for detecting~~ which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  in a subject and thereby providing a subject-specific clinical pathway for said subject, comprising a ~~decision tree~~ information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

#### **REMARKS**

Claims 1-23 were filed in the original case. Claims 1-23 were cancelled and Claims 24-44 were added in a previous amendment. Claims 24-44 were cancelled and Claims 45-71

were added in a previous amendment. Claims 69 and 70 are cancelled in the present amendment. These cancellations are made without acquiescing to the Examiner's rejections, but are made to further prosecution and Applicant's business interests. Applicant reserves the right to prosecute Claims 69 and 70 (or similar claims) in the future. Claims 45-48 and 71 are presently amended. Therefore, Claims 45-68 and 71 are currently pending.

In the Office Action dated July 8, 2003 the Examiner has made three rejections. The currently pending rejections are:

- 1) Claims 46-48, 71 stand rejected under 35 U.S.C. 112, first paragraph;
- 2) Claims 45-68, 71 stand rejected under 35 U.S.C. 112, second paragraph; and
- 3) Claims 45, 48-68, 71 stand rejected under 35 U.S.C. 102(b).

Applicant believes that the pending Claims are fully supported, definite, and are not taught by the prior art. Therefore Claims 45-68, 71 should be passed into allowance.

## REJECTIONS

For clarity, the rejections at issue are set forth by number in the order they are herein addressed.

### I. THE SPECIFICATION FULLY SUPPORTS THE CLAIMS

The Examiner has rejected Claims 46-48, and 71 under 35 U.S.C. 112, first paragraph "... as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action 7/8/2003, page 3). Applicant respectfully disagrees. The Examiner argues: "The amendment fails to point to any support in the specification for the newly added language. However, the specification does not appear to describe or discuss "a computer readable medium" and a "decision tree". The concept of a computer readable medium" and a "decision tree" does not appear to be part of the originally filed invention. Therefore a computer readable medium" and a "decision "tree" constitutes new matter. Applicant is required to cancel the new matter in reply to this office action." (Office Action 7/8/2003, page 3.)

To the contrary, the Specification provides ample, specific and detailed support for the Claims. Several non-limiting examples are provided below:

“Assays for detection of polymorphisms or mutations fall into several categories, including, but not limited to direct sequencing assays, fragment polymorphism assays, hybridization assays, and *computer based data analysis*.” (Specification, II. “Assays for Generating Genomic Profiles”, page 40. Emphasis added.)

“In some embodiments of the present invention, *perioperative genomic profiles are generated using computer-based data analysis* of a genetic information sample (e.g., stored nucleic acid sequence information). A sample is collected from a subject at anytime (e.g., at birth), sequence information is generated (e.g., through DNA sequencing), and *the information is stored (e.g., as digital information on a portable chip)*. During the perioperative period, *the subject's sequence information is scanned by a computer program* for the pre-selected markers. A report (e.g., a perioperative genomic profile) is generated.” (Specification II.E., “Computer-Based Data Analysis”, page 49. Emphasis added.)

“In some embodiments of the present invention, *the data is generated, processed, and/or managed using electronic communications systems* (e.g., Internet-based methods). In some embodiments, *a computer-based analysis program* is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease).” (Specification, III. “Analysis and Delivery of Data”, page 50. Emphasis added.)

“Where the sample comprises previously determined genetic information (e.g., sequence information, SNP or mutation information, etc.), the information may be directly sent to the genomic profiling service by the subject (e.g., a information card containing the genetic information may be *scanned by a computer and the data transmitted to a computer* of the genomic profiling center using an electronic communication systems). Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical

or surgical procedure the subject will undergo.” (Specification, III. “Analysis and Delivery of Data”, pages 50-51. Emphasis added.)

“In some embodiments, the process of selecting markers, *performing detection assays*, and distributing data to subjects and clinicians is organized by an *integrated electronic (e.g., web-based) system.*” (Specification, “Detailed Description of the Invention”, page 30. Emphasis added.)

“The present invention contemplates *any method capable of receiving, processing, and transmitting the information to and from medical personal and subject.*” (Specification III., “Analysis and Delivery of Data”, page 50. Emphasis added.)

“In some preferred embodiments of the present invention, the information generated by perioperative *genomic profiling is distributed in a coordinated and automated fashion.*” (Specification III. “Analysis and Delivery of Data, page 49. Emphasis added.)

“The fate of the sample and genomic data is driven by the subject, who is given a menu (e.g. *electronically*) of choices. . . . For example, using an *electronic communication system*, the central facility can provide data to the clinician, the subject, or researchers. . . . In some embodiments, the subject may be able to directly access the data using the *electronic communication system.*” (Specification III. “Analysis and Delivery of Data, page 51. Emphasis added.)

“The data may be displayed to the clinician by any suitable method. For example, in some embodiments, the genomic profiling service generates a report that can be printed for the clinician (e.g., at the point of care) or *displayed to the clinician on a computer monitor.*” (Specification III., “Analysis and Delivery of Data”, page 51. Emphasis added.)

“The data generated by the assay may converted to a *genomic profile in a computer system* of the emergency vehicle or may be *transmitted to distant computer system for processing.*” (Specification III., “Analysis and Delivery of Data, page 51. Emphasis added.)

In order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar

claims) in the future, Applicant has amended Claims 46-48 and 71 to recite “computer program” and “information to optimize perioperative care”.

In view of the above, Applicant requests that these rejections be withdrawn.

## **II. THE CLAIMS ARE DEFINITE**

The Examiner has rejected Claims 45-68 and 71 under 35 U.S.C. 112, second paragraph “. . . as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.” (Office Action 7/8/2003, page 4.) The Examiner argues: “The response asserts that the claimed reagents provide agents for detecting the variant alleles using the range of different technologies described in the specification.” This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require that the reagents in fact detect the presence of the variant alleles. The claim could be amended to recited “reagents which detect . . .” to overcome the rejections.”

Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner’s argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended Claims 45 and 71 to recite “reagents which detect . . .”, and “component parts which detect . . .”, respectively.

In view of the above, Applicant requests that these rejections be withdrawn.

## **III. THE CLAIMS ARE NOT ANTICIPATED**

The Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. For clarity and efficiency, because their defects as prior art are shared, and because the Examiner has cut and pasted from the Boehringer Mannheim text of the Office Action verbatim to the Perkin Elmer and Applied Biosystems text of the Office Action, the three references will be addressed together.

The text of 35 U.S.C. 102 quoted by the Examiner reads:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application in the United States.

(Office Action 7/8/2003, page 5).

Applicant respectfully asserts that the references cited by the Examiner glaringly fail to meet this standard of anticipation. To the contrary, the prior art references do **not** teach a perioperative genomic profile kit. The prior art references do **not** teach reagents which detect the presence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$* . The prior art references do **not** teach instructions for using a kit for generating a perioperative genomic profile. The prior art references do **not** teach a kit having components that provide a subject-specific clinical pathway of medical intervention if used (see e.g., Claim 71).

The Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."<sup>1</sup>

Applicant respectfully submits that not one of the catalog references cited by the Examiner teach each and every element as set forth in the claims.

In view of the above, Applicant requests that these rejections be withdrawn.

### III. A. THE CLAIMS TEACH DETECTION OF SPECIFIC VARIANT ALLELES

In response to the 1/2/2003 Office Action, Applicant pointed out to the Examiner that: "None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention." (Response to Office

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<sup>1</sup> *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

Action, filed 5/11/2003, page 9). In the present Office Action the Examiner argues: "This argument has been thoroughly reviewed, but is not found persuasive because the claim does not require detection of the variant alleles." (Office Action 7/8/2003, page 8).

Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended Claims 45 and 71 to recite "reagents which detect . . .", and "component parts which detect . . .", respectively. None of the cited references teach or suggest kits having reagents that detect the specific variant alleles.

In view of the above, Applicant requests that these rejections be withdrawn.

### **III. B. INSTRUCTIONS ARE FUNCTIONAL COMPONENTS OF THE CLAIMED KITS AND CANNOT BE IGNORED**

The Examiner has rejected Claims 45, 48-68, and 71 under 35 U.S.C. 102(b) as being anticipated by the catalogs of three manufacturers: Boehringer Mannheim; Perkin Elmer; and Applied Biosystems. Not one of the three prior art references recite "instructions for using said kit for generating said perioperative genomic profile for said subject." as recited in Claim 45, or the information to optimize perioperative care that, based at least on the presence or absence of variant alleles of two or more genes selected from the group consisting of *BChE*, *CYP2D6*, *F5*, *F2*, *CACNAIS*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TNF $\alpha$*  and *TNF $\beta$*  measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject, as recited in Claim 71. Nevertheless, the Examiner persists in re-asserting a rejection under 35 U.S.C. 102(b) only by improperly ignoring these elements. (Office Action 7/8/2003, page 8).

The Examiner argues that "In re Haller states that, in accordance with the patent statutes, an article or composition of matter, in order to be patentable, must not only be useful but must be new. *If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition regardless of the use for which it is intended.*" (Office Action 7/8/2003, page 9. Italics in original. Underline added.) In the immediately preceding Response to Office Action, Applicant pointed out

that the claimed instructions are novel, physical components dictating the manipulations of physical objects and activities which, as components of the claimed kits, implement a set of actions to accomplish a useful, concrete and tangible result. (Response to Office Action 5/11/2003, page 11). However, in the Office Action of 7/8/2003 the Examiner has conspicuously failed to respond to this statement of fact. Indeed, the Examiner concedes in the present Office Action that “The instructions are used to describe how the kit is intended to be used.” (Office Action 7/8/2003, page 9. Emphasis added). Nevertheless, the Examiner continues to confuse *In re Haller*’s “the use for which it is intended” (i.e. the kit’s purpose), with “how the kit is intended to be used”, i.e. the claimed and patentable instructions for operation of the present invention that embody functional components interacting with other components of the claimed kits in novel modes of cooperation, thereby permitting the kit’s functionality to be realized.

In consideration of *In re Gulack*, the Examiner argues “in the case of *In re Gulack*, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself, which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed kit. The components of the kit remain fully functional absent the printed instructions for use.” (Office Action 7/8/2003, page 9). The Examiner’s mischaracterizations are erroneous, and unsupported by any evidence, affidavit or other authority. To the contrary, the claimed instructions of the present invention clearly result in a structural and manipulative differences (*In re Casey*) between the manufacturer’s catalogs cited by the Examiner as prior art, and the articles and compositions of the present claims. Rather than remaining fully functional, the useful, concrete and tangible aspects of the kits of the present claims are not maintained after removal of “printed instructions for use”.

Applicant submits herewith a Declaration of Morris Waxler, Ph.D. The Declaration explains that instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. For example, without instructions approved by the Food & Drug Administration, the *in vitro* diagnostic kit is not considered functional by the Food & Drug Administration.

The Examiner argues “The intended use which is recited on the instructions lacks a functional relationship to the kit because the instructions do not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually. Therefore, the kit is unpatentable over the prior art because they function equally effectively with or without instructions, and accordingly no functional relationship exists between the instructions for use and kit components.” (Office Action 7/8/2003, page 10).

In these assertions the Examiner makes numerous errors of both fact and law. First, the Examiner’s arguments are conclusory, and unsupported by any citation to relevant case law, the MPEP, an affidavit or other authority. Second, the Examiner once again confuses the “intended use which is recited on the instructions” with “printed instructions for use”. That is, the Examiner confuses the “intended use” of a kit (its purpose) with “how to use” the kit (i.e. its operation with the physical component instructions of the claims). Indeed the Examiner tacitly acknowledges the difference in distinguishing “intended use which is recited on the instructions”, from the body (how to) of the instructions. The claimed instructions of the present invention are not a “statement of intended use”. In Claims 45 - 68 they are physical component parts of the Claims. For example, a claim to “A system of doing X, comprising component Y” is anticipated by prior art that discloses component Y for purposes other than X (i.e., use X is a statement of use the does not impart patentable weight to the claim). However, a claim that recites “A system comprising component Y and component Z, wherein component Z is configured to permit component Y to find use in process X” is patentable if the prior art does not teach the use of component Y in process X, or does not teach the use of component Z that is configured to facilitate the use of Y for X. The present claims represent the latter rather than the former example.

Third, abundant examples are proffered in the Specification of instructions which both chemically and physically affect the chemical nature of the components of the kit (See Section I.B. “Criteria for Selection of Markers”, page 32, Section I.C. “Categories of Markers”, page 34, Experimental Example 1 “Perioperative Genomic Screening for

“Anesthesia Markers”, page 53, Experimental Example 2 “Generation of Genomic Profiles”, page 57.)

Fourth, the Examiner puts forward no relevant case law, MPEP citation, affidavit or other authority in which the legal test for a functional relationship rests on whether claims “physically or chemically affect the chemical nature of the components of the kit.” (Office Action 7/8/2003, page 10). This is a standard the Examiner has made up and does not comport with the law.

Fifth, whether or not “the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually)”, (Office Action 7/7/2003, page 10), has no legal bearing on patentability.

Sixth, the Examiner’s unsupported statement that “the kit is unpatentable over the prior art because they function equally effectively with or without the instructions” is clearly erroneous. The Examiner repeats the identical mistake a second time in consideration of *In re Miller* stating “no functional relationship exists between the instructions and the other elements of the kit because the components of the kit are capable of functioning without the printed matter.” (Office Action 7/8/2003, page 10) To the contrary, as evidenced by the Declaration of Morris Waxler, Ph.D., instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to the components of the kit, and that the function of an *in vitro* genetic diagnostic kit depends on the instructions. Without instructions approved by the Food & Drug Administration, the *in vitro* diagnostic kit is not considered functional by the Food & Drug Administration, (i.e. the Food & Drug Administration recognizes the importance of the instructions to enable use of the reagents, and use of data obtained by use of the reagents in the hands of practitioners). To sustain the rejection, the Examiner must present evidence (not conclusory statements or guesses) as to the lack of a functional relationship between the claimed instructions and other components of the kits. Nor has the Examiner cited authority for the Examiner’s proposition that the test for a functional relationship is whether or not the components of the kit are capable of functioning without the printed matter. This is made-up law and does not reflect the actual law.

Finally, the Examiner argues that “Applicant’s arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a

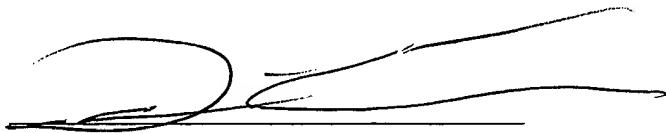
patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references." (Office Action 7/8/2003, page 11). To the contrary, in the Response to Office Action filed 5/11/2003 the Applicant expressly points out:

"None of the three references teaches variant alleles of the genes of the present invention. None of the three references teaches detection of variant alleles in two or more genes from the group of genes of the present invention. None of the three references teaches categorical criteria for the selection of genes and variant alleles of the present invention. None of the three references teaches generation of a perioperative genomic profile." (Response to Office Action, 5/11/2003, page 9).

Applicant respectfully submits that the Boehringer Mannheim, Perkin Elmer, and Applied Biosystems catalog pages cited by the Examiner do not teach each and every element of the claims as required, and requests that the rejection under 35 USC §102 be withdrawn.

It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 9/8/03



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**PATENT**

Attorney Docket No. **HOGAN-06650**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of : Kirk Hogan

Serial No.: 09/976,423

Group No.: 1634

Filed: 10/21/2001

Examiner: J.A. Goldberg

Entitled: Methods and Compositions for Perioperative Genomic Profiling

**DECLARATION OF MORRIS WAXLER, Ph.D.  
UNDER 37 CFR §1.132**

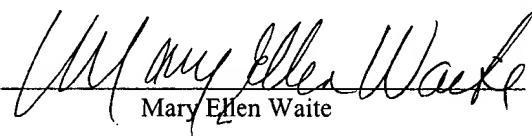
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**CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(B)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 9-8-03

By:



Mary Ellen Waite

Madam:

1. I, Morris Waxler, am a specialist in Food & Drug Administration regulatory affairs at the law firm of LaFollette, Godfrey & Kahn.

2. As a Branch Chief at the Center for Devices and Radiological Health of the Food & Drug Administration for 26 years, I am knowledgeable about Food & Drug Administration requirements for the manufacture and marketing of approved medical devices and diagnostic kits.

3. Instructions for the use of an *in vitro* genetic diagnostic kit bear a critical functional relationship to other components of the kit.

4. The function of an *in vitro* genetic diagnostic kit depends on the instructions to be approved by the Food & Drug Administration; without instructions the *in vitro* genetic diagnostic kit is not considered to be functional by the Food & Drug Administration.

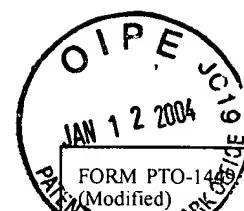
5. Therefore an *in vitro* genetic diagnostic kit does not, and cannot, function equally effectively with or without instructions.

6. The functional relationship between an *in vitro* genetic diagnostic kit and its operation is critical such that component instructions must undergo rigorous Food & Drug Administration scrutiny before the kit may be manufactured or marketed in order to assure its safety, efficacy and reliability.

7. Without Food & Drug Administration approved instructions for its operation an *in vitro* genetic diagnostic kit cannot be manufactured or marketed.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: September 7, 2003      Signed: Morris Waxler  
Morris Waxler, Ph.D.



U.S. Department of Commerce  
Patent and Trademark Office

Attorney Docket No.: HOGAN-06650

Serial No.: 09/976,423

Applicant: Kirk Hogan

Filing Date: 10/21/2001

Group Art Unit: 1634

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Examiner Initials	Cite No.	Serial / Patent Number	Issue Date	Applicant / Patentee	Class	Subclass	Filing Date

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		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation
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							No

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Examiner:

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Serial No.: 09/976,423

Applicant: Kirk Hogan

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Group Art Unit: 1634

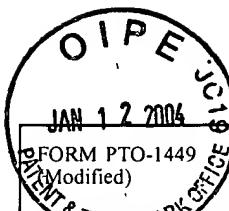
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Applicant: Kirk Hogan		
Filing Date: 10/21/2001		Group Art Unit: 1634

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(37 CFR § 1.98(b))

Applicant: Kirk Hogan

Filing Date: 10/21/2001

Group Art Unit: 1634

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Serial No.: 09/976,423

INFORMATION DISCLOSURE STATEMENT BY APPLICANT  
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(37 CFR § 1.98(b))

Applicant: Kirk Hogan

Filing Date: 10/21/2001

Group Art Unit: 1634

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			Applicant: Kirk Hogan		
			Filing Date: 10/21/2001	Group Art Unit: 1634	

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		Filing Date: 10/21/2001		Group Art Unit: 1634	
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			Applicant: Kirk Hogan	
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		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation	
							Yes	No
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FORM PTO-144 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No.: HOGAN-06650	Serial No.: 09/976,423		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use Several Sheets If Necessary)				Applicant: Kirk Hogan			
				Filing Date: 10/21/2001		Group Art Unit: 1634	
(37 CFR § 1.98(b))							

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Examiner Initials	Cite No.	Serial / Patent Number	Issue Date	Applicant / Patentee	Class	Subclass	Filing Date

## FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS

		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation
							Yes No

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FORM PTO-1449 (Modified) <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (Use Several Sheets If Necessary) (37 CFR § 1.98(b))		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No.: HOGAN-06650	Serial No.: 09/979,423		
				Applicant: Kirk Hogan			
				Filing Date: 10/21/2001	Group Art Unit: 1634		
<b>U.S. PATENT DOCUMENTS</b>							
Examiner Initials	Cite No.	Serial / Patent Number	Issue Date	Applicant / Patentee	Class	Subclass	Filing Date
		5,413,907	05/09/1995	Ronald G. Worton, <i>et al.</i>	435	6	09/21/1990
<b>FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS</b>							
		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation
		WO 99/44062	02/09/1999	PCT			Yes
		WO 02/006536	01/24/2002	PCT Search Report			No
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